Universidade Federal do Rio de Janeiro
Centro de Ciências da Saúde
Faculdade de Medicina
Programa de Pós-Graduação em Medicina
Doenças Infecciosas e Parasitárias

ESTRATÉGIAS PARA AUXILIAR NO MANEJO DA DOENÇA FÚNGICA INVASIVA E NO USO RACIONAL DE ANTIFÚNGICOS EM PACIENTES HEMATOLÓGICOS

Mariana Guaraná Macedo Moura

Rio de Janeiro
2025

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Tese de Doutorado apresentada ao Programa de Pós-Graduação em Medicina (Doenças Infecciosas e Parasitárias), Faculdade de Medicina, da Universidade Federal do Rio de Janeiro, como parte dos requisitos necessários à obtenção do título de Doutor em Medicina (Doenças Infecciosas e Parasitárias).

Orientadores: Profª. Drª. Simone Aranha Nouér
Prof. Dr. Márcio Luiz Moore Nucci

Rio de Janeiro
Setembro/2025

Moura, Mariana Guaraná Macedo
Estratégias para auxiliar no manejo da doença fúngica invasiva e no uso racional de antifúngicos em pacientes hematológicos / Mariana Guaraná Macedo Moura – Rio de Janeiro: UFRJ / Faculdade de Medicina, 2025.
115 f. ; 31 cm.

Orientadores: Simone Aranha Nouér, Márcio Luiz Moore Nucci

Tese (Doutorado) – Universidade Federal do Rio de Janeiro, Faculdade de Medicina, Programa de Pós-Graduação em Medicina (Doenças Infecciosas e Parasitárias), 2025.

Referências bibliográficas: f. 93 – 96.

1. Infecções Fúngicas Invasivas. 2. Fusariose. 3. Candidemia. 4. Educação. 5. Leucemia Aguda. 6. Medicina - Tese. I. Nouér, Simone Aranha. II. Nucci, Márcio Luiz Moore. III. Universidade Federal do Rio de Janeiro, Faculdade de Medicina, Programa de Pós-Graduação em Medicina (Doenças Infecciosas e Parasitárias). IV. Título.

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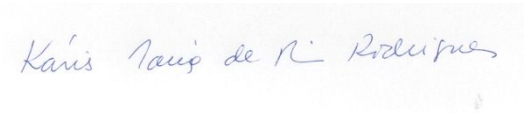

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Rio de Janeiro
Setembro/2025

DEDICATÓRIA

As mulheres que inspiram a minha vida: minha mãe Jacyana e Elisabeth que além de tia também teve um papel fundamental como mãe.

AGRADECIMENTOS

À minha família, minha mãe e aos meus irmãos, por serem meu porto seguro sempre.

Aos meus amigos, pela cumplicidade e pelo apoio nos momentos mais desafiadores.

Aos meus orientadores, Márcio e Simone, pelo conhecimento partilhado e parceria.

E à minha mulher, Camila, pelo incentivo diário e por tornar tudo mais leve.

"Você vai saber o que precisa saber quando precisar saber" - Björn Natthiko Lindeblad

RESUMO

ESTRATÉGIAS PARA AUXILIAR NO MANEJO DA DOENÇA FÚNGICA INVASIVA E NO USO RACIONAL DE ANTIFÚNGICOS EM PACIENTES HEMATOLÓGICOS

Mariana Guaraná Macedo Moura

Orientadores: Profª. Drª. Simone Aranha Nouér
Prof. Dr. Márcio Luiz Moore Nucci

Resumo da tese de doutorado submetida ao Programa de Pós-Graduação em Medicina (Doenças Infecciosas e Parasitárias), Faculdade de Medicina, da Universidade Federal do Rio de Janeiro - UFRJ, como parte dos requisitos necessários à obtenção do título de doutor em medicina (Doenças Infecciosas e Parasitárias).

Introdução: A doença fúngica invasiva (DFI) é uma complicação frequente em pacientes hematológicos. O domínio do conhecimento sobre essas infecções é essencial para um manejo eficaz e redução da mortalidade. Artigo 1: Foi avaliado o conhecimento dos hematologistas sobre infecções através de dois questionários. Obtivemos no total 289 respostas e a pontuação mediana (de 0 a 10) foi de 5,0 em ambas as pesquisas. A pontuação média baixa no geral indica uma necessidade urgente de programas de educação continuada que podem resultar no melhor atendimento ao paciente. Artigo 2: Foram comparadas 2 estratégias para profilaxia com fluconazol em pacientes com neoplasia hematológica submetidos a transplante autólogo: profilaxia precoce (iniciada com o regime de condicionamento) e tardia (iniciada somente na presença de mucosite). Candidemia ocorreu em 1,8% no grupo de profilaxia precoce, 0% no grupo de profilaxia tardia e 1,1% no grupo sem profilaxia (p=0,31). O início da profilaxia com fluconazol guiado pela ocorrência de mucosite oral foi tão bom quanto a profilaxia precoce. Artigo 3: Revisamos os fatores de risco para DFI em pacientes com LMA recebendo regimes menos intensivos baseados em venetoclax e foi proposto uma nova estratégia de risco de DFI neste grupo de pacientes. Artigo 4: Foi desenvolvida uma ferramenta para avaliar a adesão às diretrizes no tratamento da fusariose invasiva. Após revisão das recomendações atuais sobre profilaxia, diagnóstico e tratamento, criou-se uma ferramenta com 18 itens. O escore EQUAL pode ajudar os hematologistas a medirem a adesão às atuais diretrizes e melhorar o manejo da fusariose.

Palavras-chave: infecção fúngica, fusariose, candidemia, educação, leucemia aguda, antifúngico.

Rio de Janeiro
Setembro/2025

ABSTRACT

STRATEGIES TO OPTIMIZE THE MANAGEMENT OF INVASIVE FUNGAL DISEASE AND ANTIFUNGAL STEWARDSHIP IN HEMATOLOGIC PATIENTS

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Mariana Guaraná Macedo Moura

Orientadores: Profª. Drª. Simone Aranha Nouér
Prof. Dr. Márcio Luiz Moore Nucci

Abstract da tese de doutorado submetida ao Programa de Pós-Graduação em Medicina (Doenças Infecciosas e Parasitárias), Faculdade de Medicina, da Universidade Federal do Rio de Janeiro - UFRJ, como parte dos requisitos necessários à obtenção do título de doutor em medicina (Doenças Infecciosas e Parasitárias).

Introduction: Invasive fungal disease (IFD) is a frequent complication in hematological patients. Mastery of knowledge about these infections is essential for effective management and reduced mortality. Article 1: The knowledge of hematologists about infections was assessed using two questionnaires. We obtained a total of 289 responses: 223 and the median score (from 0 to 10) was 5.0 in both surveys. The overall low average score indicates an urgent need for continuing education programs that could result in better patient care. Article 2: Two strategies for fluconazole prophylaxis in patients with hematologic neoplasms undergoing autologous transplant were compared: early prophylaxis (initiated with the conditioning regimen) and late prophylaxis (initiated only in the presence of mucositis). Candidemia occurred in 1.8% in the early prophylaxis group, 0% in the late prophylaxis group, and 1.1% in the no prophylaxis group (p= 0.31). Initiating fluconazole prophylaxis guided by the occurrence of oral mucositis was as effective as early prophylaxis. Article 3: We reviewed the risk factors for IFD in patients with AML receiving fewer intensive regimens based on venetoclax and proposed a new IFD risk strategy in this group of patients. Article 4: A tool was developed to assess adherence to guidelines in the treatment of invasive fusariosis. After reviewing the current recommendations on prophylaxis, diagnosis, and treatment, an 18-item tool was created. The EQUAL score can help hematologists measure adherence to current guidelines and improve the management of fusariosis.

Key words: fungal infection, fusariosis, candidemia, education, acute leukemia, antifungal.

Rio de Janeiro
Setembro/2025

SUMÁRIO

LISTA DE SIGLAS E ABREVIATURAS

AI – Aspergilose Invasiva

CIM – Concentração Inibitória Mínima

DECH – Doença do Enxerto contra o Hospedeiro

DFI – Doença Fúngica Invasiva

EQUAL – *European Confederation of Medical Mycology QUALity Score* (Escore de Qualidade da Confederação Europeia de Micologia Médica)

EUA – Estados Unidos da América

FI – Fusariose Invasiva

GM-CSF – Fator Estimulante de Colônias de Granulócitos e Macrófagos

G-CSF – Fator Estimulante de Colônias de Granulócitos

HEPA – *High-Efficiency Particulate Air* (Ar Particulado de Alta Eficiência)

IC 95% – Intervalo de Confiança de 95%

IFI – Infecção Fúngica Invasiva

LMA – Leucemia Mieloide Aguda

LLA – Leucemia Linfoblástica Aguda

MI – Mucormicose Invasiva

PET-SCAN – *Positron Emission Tomography (PET) - Scan*

RCP – Reação em Cadeia da Polimerase

ROC – Rino-orbito-cerebral

RR – Razão de Riscos

TCH – Transplante de Células Hematopoéticas

1 INTRODUÇÃO

Doença fúngica invasiva (DFI) é uma infecção oportunista comum e grave em pacientes hematológicos nos quais o risco de infecção está relacionado tanto à imunossupressão causada pela doença de base quanto ao tratamento que engloba quimioterapia intensa, transplante de células hematopoéticas (TCH) e as novas terapias alvo.[1-4] Neste cenário, os indivíduos de maior risco são aqueles com leucemias agudas e os submetidos a TCH alogênico devido a neutropenia prolongada, que é o principal fator de risco para DFI.[5, 6]

Entre os fungos mais comuns envolvidos na DFI em pacientes hematológicos estão os gêneros *Aspergillus* e *Candida*, que representam a maioria dos casos.[7, 8] No entanto, a incidência pode variar dependendo da localização geográfica, do uso de profilaxia antifúngica e infecções por fungos emergentes, como Mucorales e *Fusarium* spp. [9, 10]

No Brasil, a aspergilose invasiva (AI) é a principal DFI em pacientes hematológicos, seguido da fusariose e da candidíase invasiva.[11] Entre as principais espécies que causam AI, o *Aspergillus fumigatus* é a mais frequente.[12] Por outro lado, na candidemia as espécies de *Candida não*-albicans têm incidência crescente devido ao uso de fluconazol profilático, estratégia introduzida no início dos anos 90.[2, 13]

As manifestações clínicas da DFI podem variar de acordo com o agente etiológico, o estado imunológico do paciente e o local da infecção.[12, 14, 15] Nas infecções por fungos filamentosos, febre e sintomas respiratórios são mais comuns, exceto na fusariose onde o quadro clínico é marcado pela presença de lesões de pele.[14] Na candidíase invasiva, as infecções geralmente se manifestam como candidemia ou, mais raramente, como candidíase disseminada crônica.[16, 17]

A mortalidade associada a DFI em pacientes hematológicos permanece elevada, mesmo com os avanços na terapia antifúngica. [5, 18] A taxa de mortalidade pode variar dependendo do tipo de fungo envolvido, da extensão da infecção e do tempo até início do tratamento. Pacientes com aspergilose invasiva podem apresentar

taxas de mortalidade superiores a 50%, e na mucormicose entre 40 e 80%, especialmente se o diagnóstico e tratamento forem tardios.[19]

A prevenção e o manejo eficaz dessas infecções continuam sendo desafiadores, destacando a necessidade de estratégias profiláticas e diagnósticas aprimoradas, além de novos agentes antifúngicos que possam aumentar as chances de sobrevida desses pacientes vulneráveis.[1, 20, 21]

Nos últimos anos, apesar da evolução nas práticas do uso de antifúngicos, a DFI continua a ter impacto negativo no prognóstico de pacientes hematológicos, com elevada taxa de mortalidade.[18, 22] Portanto, torna-se fundamental a atualização frequente e contínua em temas sobre epidemiologia, agentes etiológicos predominantes e as manifestações clínicas da DFI para o adequado manejo dos pacientes neutropênicos com neoplasias hematológicas.

2 REVISÃO DA LITERATURA

2.1 Epidemiologia da doença fúngica invasiva em pacientes hematológicos

As infecções fúngicas mais frequentes em pacientes com neoplasias hematológicas são a candidíase invasiva, a aspergilose, a fusariose e a mucormicose.[6, 23] A incidência desses patógenos varia entre 2% e 49%, sendo esta grande variação atribuída a populações diferentes (doença de base, tipo de tratamento) e pela localização geográfica, que tem importante impacto na epidemiologia da DFI.[24]

Até os anos 2000, a candidíase invasiva era a principal causa de DFI em pacientes oncohematológicos, principalmente causada pela espécie *Candida albicans*.[25] No entanto, dois fatores contribuíram para uma mudança na epidemiologia das infecções fúngicas: (1) o aumento no uso de antifúngicos profiláticos no início dos anos 90 e (2) o surgimento das estratégias de terapias empírica e preemptiva.[26] Após a introdução do fluconazol profilático nos protocolos quimioterápicos, houve uma importante redução na frequência de infecções por

Candida spp., assim como mudança nas espécies mais prevalentes. Na era pré-fluconazol, o predomínio era de *Candida albicans*, porém, após a introdução dos azólicos, outras espécies emergiram como *C. glabrata* e *C. krusei*.[27] Um estudo publicado em 2009, mostrou declínio nas infecções causadas por *C. albicans*, de 34% entre 1988-1992 para 24% em 2001-2007 em um centro nos Estados Unidos da América e que a etiologia de 76% das candidemias analisadas eram de *Candida* não-albicans.[28] Apesar da diminuição na incidência, a candidemia ainda está associada a elevadas taxas de morbidade e mortalidade, além de contribuir com um tempo prolongado de internação.[29] .Além disso, entre as espécies de *Candida spp.*, a *C. krusei* é responsável por uma taxa de óbito alta (52,9%).[13, 30]

Atualmente, infecções por fungos filamentosos representam a principal causa de DFI, com frequência de 11-18% em pacientes com leucemia mieloide aguda (LMA) e entre 5-10% naqueles que recebem TCH alogênico.[31] Neste cenário, o *Aspergillus spp.* é o principal patógeno no Brasil e no mundo, com uma frequência de até 24% em pacientes com LMA e mielodisplasia.[32-34] Entre as espécies mais frequentes na AI, estão o *A. fumigatus* e o *A. flavus*. Um estudo desenvolvido na França avaliou 127 casos de AI no período de 2004 e 2008 e mostrou que das amostras de cultura positivas, *A. fumigatus* estava presente em 55%, *A. flavus* em 17% e *A. niger* em 10%.[35] Por outro lado, em regiões de clima tropical como Arábia Saudita, Sudão e na África, *A. flavus* é a espécie mais comum em casos de aspergilose invasiva.[36] Um estudo prospectivo realizado em um centro na Tunísia analisou a prevalência de *Aspergillus* spp. no meio ambiente e, a partir de 1680 amostras, espécies de *Aspergillus* spp. foram isolados em 130 casos, dos quais 79,2% eram *A. flavus*, 10% *A. niger* e apenas 2,3% eram *A. fumigatus*.[37] Portanto, clima e fatores geográficos têm impacto importante na epidemiologia, contribuindo para mudança na frequência das espécies, sendo então fundamental o conhecimento da epidemiologia local de cada centro.[38]

A mortalidade associada a AI em pacientes com leucemia aguda e receptores de TCH alogênico é de 30 a 40% e 35 a 56%, respectivamente.[5, 39] Apesar de alta, com o avanço nos exames laboratoriais, o diagnóstico precoce e tratamento adequado, a mortalidade tem diminuído nos últimos anos.

Infecções por *Fusarium* spp. e zigomicetos são menos frequentes e com variação na incidência a depender da região geográfica.[9, 40, 41] No entanto, uma característica comum à fusariose e à mucormicose é o prognóstico ruim, com

mortalidade entre 50 e 70%.[42, 43] Na fusariose, as espécies que mais frequentemente causam infecção em humanos são aquelas do complexo *Fusarium solani* e *Fusarium oxysporum*.[43] Na mucormicose, os patógenos mais frequentes são *Rhizopus* spp., seguido de *Mucor* spp. e *Lichtheimia* spp., porém pode haver variação na prevalência de acordo com localização geográfica.[44, 45] Uma meta-análise que incluiu 851 pacientes com mucormicose, 33% tinham neoplasia hematológica e, *Rhizopus* spp. foi o agente etológico mais frequente.[46]

2.2 Doença fúngica invasiva no Brasil

No Brasil, a incidência da DFI em pacientes onco-hematológicos é de 10 a 13% e varia de acordo com a doença de base sendo maior o risco em pacientes com LMA.[11, 33, 47] Em um estudo prospectivo com 8 centros, Nucci e cols. encontraram uma incidência cumulativa em um ano de 18,7%, 11,3% e 1,9% em pacientes com LMA, após TCH alogênico e autólogo, respectivamente. Além disso, a DFI mais frequente foi a fusariose seguida de aspergilose.[47] No entanto, uma importante limitação deste estudo foi que o exame da galactomanana não estava disponível em grande parte do período do estudo, o que pode ter colaborado para um viés, com redução nos casos de aspergilose provável.[47] Em 2021, Souza e cols. revisitaram este tema num estudo prospectivo em quatro centros brasileiros onde galactomanana e exames de imagem foram realizados de rotina para o diagnóstico de DFI.[11] Foi observada uma alta frequência de DFI em pacientes com LMA (26,1%) e em leucemia linfoide aguda (LLA, 16,7%), sendo AI a principal infecção (7,3%) seguido de candidemia e fusariose (1.3%).[11] É importante destacar que este estudo confirmou a baixa incidência de mucormicose (0,5%), comparada com outros países [48, 49] e uma sobrevida em 30 dias menor em pacientes com DFI comparado com quem não desenvolveu DFI.

Em muitos centros no Brasil, a profilaxia antifúngica utilizada é o fluconazol, associada à estratégia de diagnóstico guiada pelo uso de ferramentas como galactomanana e exames de imagem.[50] Em 2021, Bergamasco e cols.[51], analisaram retrospectivamente casos de DFI provável e provada no período de 2009 a 2019 em único centro brasileiro, onde era utilizado esta estratégia. A frequência de DFI em pacientes com leucemia aguda e em receptores de TCH alogênico foi de

17,3% e 8,9%, respectivamente. Neste estudo, a aspergilose invasiva também foi a principal causa de DFI, porém, ao contrário do estudo de Souza e cols., fusariose foi a segunda DFI mais frequente, seguida de candidíase invasiva. Um dado interessante foi a frequência de criptococose, com 8,5% em pacientes com doença linfoproliferativa, confirmando o que já foi descrito anteriormente sobre maior incidência criptococose neste grupo de doenças, especialmente com o uso de novos medicamentos como os inibidores da bruton quinase.[51, 52]

A incidência de fusariose em pacientes hematológicos varia de acordo com as regiões ao redor do mundo, e mesmo entre diferentes centros no mesmo país.[43] Porém, comparado com outros países na Europa e nos Estados Unidos da América (EUA), o Brasil apresenta incidência da fusariose mais alta, variando entre 1,6-1,7%, podendo chegar a 4,3% em pacientes com LMA e 3,1% após TCH alogênico de medula.[11, 43, 51] Por ouro lado, estudos italianos mostraram uma frequência entre 0,1 e 1,7% e, nos EUA 0,7% em receptores de TCH (1,2% no alogênico e 0,2% no autólogo).[5, 40, 53]

A primeira descrição de fusariose invasiva no Brasil foi publicada em 1992 por Nucci e cols. no qual apresentaram as manifestações clínicas típicas e o diagnóstico através da hemocultura em pacientes com doença disseminada.[54] Em 2003, o mesmo autor, mostrou a mortalidade alta associada a fusariose invasiva nos pacientes com neoplasias hematológicas, assim como os fatores associados com pior prognóstico.[55] Dos 84 casos analisados, somente 50% e 21% dos pacientes estavam vivos 30 e 90 dias após o diagnóstico de fusariose, respectivamente.[55] Na análise multivariada, neutropenia e uso de corticoide foram os dois fatores associados com desfechos ruins e impacto na sobrevida. Em 2004, um outro estudo que incluiu 9 centros, caracterizou a epidemiologia e os fatores prognósticos da fusariose invasiva em pacientes hematológicos submetidos a TCH.[56] Nucci e cols., mostraram que a incidência de fusariose no TCH alogênico com antígenos leucocitários humanos (HLA)- incompatível pode ser quatro e 10 vezes maior que em pacientes submetidos a TCH HLA compatível e autólogo, respectivamente. Outro dado importante foi a descrição da distribuição trimodal da infecção por *Fusarium*, com o primeiro pico antes da recuperação neutrofílica, o segundo que ocorre próximo dos 60 dias após o TCH e o terceiro que é mais tardio, um ano após o TCH.[56]

Com relação à infecção por *Candida* spp. em pacientes hematológicos, estudos brasileiros apontam que a epidemiologia é também diferente de outros países.[57, 58] Bergamasco e cols. caracterizaram os episódios de candidemia em pacientes hematológicos e com tumores sólidos de 18 centros na América Latina.[59] As espécies encontradas mais frequentemente foram *C. albicans*, seguido *C. tropicalis* e *C. parapsilosis*. Quando comparado os dois grupos, a incidência de infecção por *C. parapsilosis* foi maior nos pacientes com neoplasias hematológicas, e estava provavelmente relacionada a uso de cateter e de fluconazol profilático que poderia reduzir a colonização por *Candida* spp., no trato gastrointestinal.[59] Por outro lado, infecção por *C. glabrata* e *C. krusei* foram infrequentes.

As condições geográficas, as práticas de profilaxia antifúngica e a ausência de proteção ambiental com filtro do tipo *High-Efficiency Particulate Air* (HEPA) podem contribuir para a alta incidência de DFI no Brasil, principalmente em pacientes com leucemia aguda e submetidos a TCH alogênico. Estratégias que mitiguem esses riscos podem auxiliar na redução do risco de DFI em nosso país.

2.3 Fatores de risco

Neutropenia é um dos fatores de risco mais associados a DFI, principalmente aquelas causadas por fungos filamentosos.[60] Mais importante ainda é a duração e intensidade da neutropenia, sendo os pacientes de maior risco aqueles com leucemia aguda tratados com quimioterapia intensa e os submetidos a TCH alogênico.[61, 62]

Identificar os parâmetros antes e durante o tratamento que podem predizer a duração da neutropenia é essencial para estratificar o risco de DFI em pacientes hematológicos, principalmente causadas por fungos filamentosos.[63] Deve-se considerar fatores relacionados ao hospedeiro, a doença de base e a exposição ambiental.[64] Na LMA, citogenética desfavorável, contagem de leucócitos elevada ao diagnóstico, comorbidades e idade avançada (mais do que 65 anos) são variáveis que impactam na probabilidade de remissão completa durante o tratamento e, portanto, predizem um tempo de neutropenia mais prolongado e risco maior de infecção fúngica.[63, 65, 66] Variáveis relacionadas ao hospedeiro como

sobrecarga de ferro, uso prolongado de corticosteroides, hiperglicemia e tabagismo também contribuem para o risco aumentado de DFI.[64, 67, 68] Além disso, colonização por *Aspergillus* spp., internação em ambiente hospitalar sem filtro HEPA ou com obra, também aumentam o risco de aspergilose.[69-71]

Em 2010, Chabrol e cols., analisaram retrospectivamente 257 pacientes com leucemia aguda e identificaram que doença pulmonar prévia, neutropenia ao diagnóstico e LMA com citogenética de alto risco eram fatores de risco para aspergilose invasiva, enquanto profilaxia primária era protetor.[72] Na fusariose invasiva, em uma série de 84 casos diagnosticados em centros do Brasil e dos EUA, 83% dos pacientes estavam neutropênicos ao diagnóstico da fusariose e quase todos os casos ocorreram em indivíduos com leucemia refratária ou recaída.[55] Nesta análise, neutropenia persistente (razão de riscos [RR] 5,43; intervalo de confiança [IC] 95% 2,64-11,11) e uso de corticosteroides (RR 2,18 IC 95% 1,98-3,96) foram fatores de mau prognóstico.[55] Diferente dos pacientes com leucemia aguda, nos receptores de TCH alogênico, a fusariose pode ocorrer mesmo na ausência de neutropenia. No cenário do TCH após a recuperação medular, a imunodeficiência celular causada pela doença do enxerto contra hospedeiro (DECH) e seu tratamento são os fatores que mais contribuem para o risco de DFI.[73] Um estudo com 84 pacientes no TCH alogênico, mostrou que a fusariose invasiva tinha uma distribuição trimodal: um pico de incidência nos primeiros 30 dias (antes da pega da medula), segundo momento entre os dias 61 e 80 após o TCH, e o terceiro pico após os 360 dias.[55] Com exceção do primeiro momento, nos outros dois a infecção pode ocorrer no contexto de DECH aguda e crônica.[56] Em uma coorte retrospectiva com 11.980 pacientes, Riches e cols. analisaram 124 casos de DFI excluindo aspergilose, e encontraram que DECH, idade maior do que 50 anos e infecção prévia por *Aspergillus* spp., eram fatores de risco para mucormicose.[42]

Com relação a candidemia em pacientes hematológicos, o principal fator de risco é a presença de mucosite.[74] *Candida* spp., é um patógeno que coloniza o trato gastrointestinal e, portanto, a quebra de barreira mucosa decorrente do uso de quimioterapia intensa ou de DECH gastrointestinal aumentam o risco de translocação e candidíase invasiva.[74]

Nucci e Anaissie discutiram a origem da candidemia, se é pela presença de cateter ou do trato gastrointestinal e mostraram que a maior parte das infecções

ocorrem por translocação e que não há a necessidade de remoção precoce de cateter em casos de candidemia.[75]

2.4 Manifestações clínicas

Nos pacientes imunocomprometidos, a principal porta de entrada dos fungos filamentosos como *Fusarium*, *Aspergillus* e os agentes da mucormicose é a via respiratória, através da inalação.[76, 77] No entanto, a quebra de barreira na pele, através de lesões, também é uma via de entrada para *Fusarium* e *Mucor*, sendo a forma cutânea da mucormicose encontrada mais frequentemente em pacientes vítimas de trauma ou queimados.[78] Portanto, de forma geral, uma das principais manifestações clínicas da DFI por estes fungos é o acometimento pulmonar. Por outro lado, as infecções causadas por *Candida* spp. decorrem da translocação do trato gastrointestinal quando há mucosite levando à candidemia.[75]

A fusariose invasiva (FI) pode ser adquirida na comunidade ou em ambiente hospitalar. Neste último, a contaminação ocorre através da inalação do ar ou por água contaminada (contato com lesão em pele ou inalação de aerossol).[79-81] Além da febre, as principais manifestações clínicas incluem: lesão de pele, pneumonia, celulite ou linfangite onda há quebra de barreira na pele por onicomicose ou intertrigo digital.[55] Uma análise de 232 casos de FI em pacientes imunossuprimidos, mostrou que 72% dos pacientes tinham lesões de pele disseminadas.[82] Além disso, caracterizaram as lesões como pápulas ou nódulos, com ou sem necrose em diferentes estágios de evolução, e que muitas vezes estavam associadas a mialgia.[82] A pneumonia causada por *Fusarium*, em geral, ocorre como doença disseminada, sendo esta apresentação mais comum em pacientes nos quais a pele é a porta de entrada e a disseminação é hematogênica.[83] Nucci e cols. analisaram 233 casos de FI e destes, 114 pacientes tinham acometimento pulmonar, sendo que em 105 casos a pneumonia fazia parte de um quadro disseminado e somente em nove pacientes era uma doença localizada no pulmão.[83] Neste mesmo estudo, outra manifestação clínica frequente foi sinusite, que estava presente em 72 (31%) dos 233 casos de fusariose, e na maioria dos pacientes fazia parte de doença disseminada.[83] A fungemia é a forma de apresentação clínica mais frequente da FI, presente em mais de 50% dos pacientes

hematológicos ao diagnóstico e com mortalidade elevada.[55] É importante destacar que no contexto do TCH alogênico de medula, outras manifestações menos típicas podem ocorrer, como artrite e endoftalmite.[84, 85]

Na AI, o paciente hematológico de alto risco pode se apresentar com febre persistente apesar do uso de antibióticos, ou mesmo não apresentar febre.[77] O acometimento pulmonar é o mais comum e apresenta duas fases: broncoalveolar, mais precoce, e angioinvasiva, que se caracteriza por infarto pulmonar (12). A expressão radiológica na fase broncoalveolar se caracteriza pela presença de infiltrados tipo ‘árvore em brotamento’, vidro fosco e consolidação peri-brônquica, e na fase angioinvasiva, por nódulo com ou sem ‘sinal do halo’ e consolidação.[86] Colombo e cols., compararam as manifestações clínicas da AI de 77 pacientes com LMA e LLA e mostraram que febre e acometimento pulmonar estavam presentes em 89,6% e 92,2% dos casos, respectivamente.[87] Além disso, sinusite, outra manifestação comum da AI, estava presente em 29,9% dos pacientes.[87]

A aspergilose, assim como a fusariose, compartilham um contexto epidemiológico semelhante, porém, com características clínicas e laboratoriais que podem ser diferentes.[88] Nucci e cols., revisaram 36 casos de pacientes com AI e 26 com FI e encontraram algumas diferenças.[88] Febre foi mais frequente nos casos de FI comparado com AI (96,2% *versus* 63,9%; p=0,003), mas pneumonia (88,9% *versus* 50,0%; p=0,001) e sinusite (63,9% *versus* 38,5%; p=0,048) foram mais comuns na aspergilose. Por outro lado, lesão de pele e fungemia com hemocultura positiva foram manifestações encontradas exclusivamente na fusariose. Com relação ao diagnóstico, o ‘sinal do halo’ estava mais presente nos pacientes com AI, no entanto, não houve diferença em relação a galactomanana positiva (88,6% na AI e 73,3% na FI; p=0,18).[88]

A mucormicose invasiva (MI) pode se apresentar clinicamente com diferentes padrões: (1) pulmonar, (2) rino-orbital-cerebral, (3) gastrointestinal, (4) disseminada, (5) cutânea e outras formas raras.[45] Ao contrário dos imunocompetentes, nos pacientes com neoplasias hematológicas as apresentações clínicas mais comuns são o acometimento pulmonar, a rino-orbital-cerebral (ROC) e a disseminada.[89, 90] Uma análise de 604 casos de MI em pacientes com neoplasias hematológicas ou submetidos a TCH alogênico mostrou que as formas mais frequentes de MI foram pulmonares (44.4%), ROC (27,6%) e disseminada (16%).[45] Febre, assim como em outras DFI, é a manifestação clínica mais frequente. A tríade de tosse, dispneia e

dor torácica está associada com apresentação pulmonar da doença. Na forma ROC, dor nos seios paranasais e olhos, rinorreia, congestão nasal são sinais de alerta assim como úlcera nasal ou no palato e proptose são sinais de doença avançada. [91] Nos exames de imagem, sinais sugestivos de MI são a presença do 'halo reverso', cavitação no pulmão e espessamento mucoso, obliteração dos seios paranasais e destruição óssea na forma ROC.[45]

Diferente dos fungos filamentosos, as infecções por *Candida* nos pacientes hematológicos tem origem no trato gastrointestinal e se manifesta principalmente como candidemia após quebra de barreira por mucosite e translocação.[75] Não há sinal ou sintoma específico de candidíase invasiva, porém em pacientes com fatores de risco (neutropenia, mucosite), febre persistente e que não estão em uso de profilaxia antifúngica, deve-se suspeitar de infecção por *Candida*.[92] No entanto, alguns pacientes podem apresentar lesões de pele que em geral estão associadas a candidemia por *C. tropicalis*. [93] Uma revisão sistemática publicada em 2018, analisou 100 casos de candidíase em pacientes neutropênicos com lesão de pele e descreveu dois padrões: (1) lesões maculopapulares disseminadas em pacientes com *C. tropicalis* que não estavam em uso de profilaxia antifúngica e, (2) lesões nodulares e/ou papulares por *C. krusei* em pacientes em uso de fluconazol profilático.[94] A mortalidade em indivíduos com candidemia e lesão de pele foi de 45,4%.[94] Além da candidemia, outra apresentação clínica é a candidíase disseminada crônica. Nestes casos, o quadro mais comum é o de febre persistente após recuperação dos neutrófilos, dor no quadrante superior direito do abdome, náusea e hepatoesplenomegalia cujo exame de imagem mostra múltiplas pequenas lesões no baço e no fígado.[95]

Portanto, apesar do quadro clínico diferente entre esses principais fungos, o conhecimento dos fatores de risco, do perfil do hospedeiro e das características clínicas das doenças fúngicas auxiliam para um diagnóstico mais adequado e rápido na beira do leito.

2.5 Diagnóstico da doença fúngica invasiva

De acordo com a organização europeia para pesquisa e tratamento do câncer (EORTC), a DFI pode ser definida como possível, provável ou provada.[96] Em todas as definições devem ser considerados os fatores do hospedeiro como: neutropenia prolongada, neoplasia hematológica, transplantados de órgãos sólidos ou de medula, uso prolongado de corticosteroide ou com DECH.[96, 97] Além disso, os pacientes também devem apresentar características clínicas sugestivas de DFI que incluem a presença de imagem radiológica. No entanto, para definir DFI provável, além destes critérios, é necessário também ter evidência micológica como cultura do escarro ou lavado broncoalveolar, microscopia direta mostrando a presença do fungo, reação em cadeia de polimerase (RCP) para *Aspergillus* ou galactomanana positiva (antígeno presente na parece celular dos fungos). Para DFI provada é fundamental a documentação da infecção fúngica em um tecido estéril por cultura, histopatológico ou hemocultura positiva (nos casos de *Candida* e *Fusarium*).[96, 97] Tal classificação foi criada para homogeneizar o recrutamento de pacientes em estudos clínicos, mas não para o cuidado de pacientes.

Portanto, as ferramentas utilizadas para o diagnóstico de DFI incluem exames radiológicos, cultura (sangue, secreção pulmonar), histopatológico e biomarcadores como galactomanana, beta-glucana e a reação em cadeia de polimerase.[97-99] A pesquisa de anticorpos para aspergilose possui sensibilidade baixa pela incapacidade do hospedeiro de desenvolver uma resposta humoral com formação de anticorpos e, por isso, não é utilizado no cenário da hematologia. Por outro lado, o exame da galactomanana é fundamental para o diagnóstico e acompanhamento da DFI em pacientes neutropênicos. O teste pode detectar precocemente a infecção fúngica e pode ser realizado no sangue, lavado broncoalveolar e líquor, sendo considerado como ponto de corte ≥0,5, ≥1,0 e ≥1,0, respectivamente.[86, 100, 101] O acompanhamento da cinética da galactomanana também é importante para monitorar o tratamento da DFI e está associada a um bom desfecho se os valores normalizam dentro de uma a duas semanas do início da terapia antifúngica, o que significa que houve redução na carga fúngica do paciente.[102] Durante o tratamento dos pacientes hematológicos de alto risco, a galactomanana seriada (duas a três vezes por semana) é utilizada em conjunto com exames radiológicos

como estratégia para terapia antifúngica preemptiva.[103] No entanto, deve-se destacar que o teste pode ser positivo tanto na aspergilose como na fusariose, sendo a sensibilidade é reduzida quando está sendo utilizada profilaxia antifúngica para fungo filamentoso.[104, 105] Por outro lado, uma galactomanana negativa em um paciente com alterações clínicas e radiológicas sugestivas de DFI, deve-se suspeitar de mucormicose.[106] Outro teste que pode ser utilizado é a detecção da 1,3-beta-D-glucana, útil no diagnóstico de candidíase, aspergilose, fusariose e pneumocistose, porém tem limitações como baixa disponibilidade nos centros e taxa alta de falso positivo.[106, 107]

Além dos biomarcadores já conhecidos, galactomanana e 1,3-beta-D-glucana, nos últimos anos surgiram os exames de RCP para *Aspergillus*, Fusarium e Mucor.[98, 108, 109] Porém devem ser utilizados com cautela. No paciente neutropênico, o RCP para *Aspergillus* tem alta sensibilidade e elevado valor preditivo negativo sendo um bom teste para vigilância, capaz de diagnosticar a AI de forma precoce, mesmo antes da galactomanana ser positiva.[110] Além disso, existem alguns testes de RCP que podem detectar as espécies de *Aspergillus* com resistência adquirida aos azólicos.[110] Entretanto, o RCP tem limitações como a baixa sensibilidade em pacientes não neutropênicos ou em uso de profilaxia antifúngica, é dependente da correlação clínica e radiológica podendo ser positivo em pacientes colonizados, a ausência de padronização em larga escala e a indisponibilidade de testes em muitos centros.[110] Apesar de não estar incluído como critério diagnóstico, a RCP também tem auxiliado no diagnóstico precoce da mucormicose com estudos mostrando que o teste é positivo dias antes do surgimento da imagem radiológica.[111] No estudo MODIMUCOR de Millon e cols., no qual avaliaram o uso de RCP no sangue para diagnóstico de mucormicose, a sensibilidade, especificidade, valor preditivo positivo e negativo da RCP no sangue para a detecção dos gêneros *Lichtheimia*, *Rhizomucor*, e *Mucor/Rhizopus* foram de 85,2%, 89,8%, 52,3% e 97,9%, respectivamente, e os pacientes que tiveram persistência da RCP positiva após início do tratamento antifúngico tiveram desfecho pior.[112, 113] No entanto, assim como na AI, a principal limitação é a ausência de padronização, custo e baixa disponibilidade do teste nos centros.[108] Outro método não invasivo que tem se mostrado uma valiosa ferramenta no diagnóstico de infecções em pacientes hematológicos é sequenciamento de próxima geração aplicado a metagenômica que identifica o DNA de bactérias, fungos e vírus e pode ser analisado em amostras de

sangue ou no lavado broncoalveolar.[114] Fu e cols., compararam o uso do sequenciamento por metagenômica com métodos convencionais (microscopia direta, galactomanana, cultura) no diagnóstico de infecções pulmonares em pacientes submetidos a TCH alogênico e encontraram uma sensibilidade superior de 88,8% x 69,4% e especificidade de 81,0% x 85,7%, respectivamente.[115] As vantagens da metagenômica incluem também a identificação de bactérias resistentes, rapidez no diagnóstico e auxiliar na identificação de infecções por patógenos raros.[116, 117] Por outro lado, as limitações incluem o custo alto, a disponibilidade nos centros e assim como outros métodos, a correlação com o quadro clínico.[117]

A tomografia de alta resolução é também uma importante ferramenta para o diagnóstico de DFI.[118] No tórax, imagens como ‘sinal do halo’, opacidades centrolobulares, ‘sinal do ar crescente’, consolidação lobar, cavitações e ‘sinal do halo invertido’ são sinais de infecção fúngica.[69, 119, 120] Além disso, espessamento mucoso com áreas de necrose nos seios paranasais ou nódulos no baço ou fígado podem sugerir infecção por fungo filamentoso e candidíase, respectivamente.[120] Apesar de não ser patognomônico de AI, em um contexto clínico e epidemiológico compatível, o ‘sinal do halo’ é muito sugestivo de aspergilose e corresponde a uma área de infarto pulmonar (nódulo) circunscrita por edema e hemorragia (vidro fosco).[121] Por outro lado, o ‘sinal do halo reverso’, encontrado na mucormicose, é a imagem radiográfica de um vidro fosco rodeado por um anel de consolidação.[121] Nos últimos anos, a tomografia com emissão de pósitrons (PET-SCAN) tem auxiliado no manejo da DFI, principalmente para estadiamento e monitoramento.[122] No entanto, tem como limitações o alto custo, não é ideal para detectar lesões cerebrais, no rim ou coração e tem baixa especificidade.[122]

2.6 Tratamento das doenças fúngicas mais frequentes

2.6.1 Candidemia

As equinocandinas, caspofungina, micafungina, anidulafungina ou rezafungina, são consideradas a terapia de primeira linha no tratamento da candidemia.[123] O início precoce do antifúngico adequado tem impacto na sobrevida dos pacientes e reduz a mortalidade.[92] Após a identificação da espécie, o teste de susceptibilidade deve guiar o tratamento e, se sensível a fluconazol, pode ser realizado o descalonamento caso o paciente esteja estável clinicamente, após alguns dias de terapia endovenosa.[123, 124] A depender de algumas espécies de *Candida*, o tratamento de escolha pode mudar, como nas infecções por *C. krusei* que é intrinsecamente resistente ao fluconazol mas não ao voriconazol.[63] Outra opção de tratamento é a anfotericina lipossomal, porém deve ser considerada como alternativa caso exista contraindicação ao uso de equinocandina. A candidíase disseminada crônica é tratada da mesma forma que a candidemia.

2.6.2 Aspergilose invasiva

Atualmente há três classes de antifúngicos disponíveis para tratamento da AI: azólicos, polienos e as equinocandinas.[125]

Na primeira linha, os melhores níveis de evidência com recomendação A-I são os triazólicos: voriconazol e isavuconazol.[126, 127] O primeiro, tem taxas de resposta descritas na literatura entre 36 e 52,8%, está associado a redução na duração da internação e é um medicamento com boa penetração no sistema nervoso central e olhos.[126, 128, 129] Os efeitos colaterais mais frequentes são hepatotoxicidade, alterações visuais e psiquiátricas (incluindo alucinação), fototoxicidade e periostite em pacientes submetidos a tratamentos prolongados.[130, 131] Outro ponto de atenção com o voriconazol é a farmacocinética variável, sendo importante o acompanhamento do nível sérico.[132] O isavuconazol, é também considerado terapia de primeira linha com o mesmo nível de recomendação após um estudo de não inferioridade mostrar que o medicamento é tão eficaz quanto o voriconazol no

tratamento da AI, sem diferença na sobrevida.[123, 133] No entanto, quando analisado o perfil de segurança, isavuconazol tem menos efeitos colaterais e a farmacocinética é mais linear, não sendo obrigatório a dosagem do nível sérico.[133] O posaconazol foi comparado ao voriconazol em um estudo randomizado de não inferioridade e os resultados mostraram ausência de diferença com relação a mortalidade e menos efeitos colaterais com posaconazol, sendo este também uma opção de tratamento para AI apesar de ser usado com mais frequência como profilaxia. Um problema comum a todos os azólicos são as interações medicamentosas uma vez que esses medicamentos são inibidoras do citocromo P450 e das P-glicoproteínas com diferentes intensidades.[134] Como muitos medicamentos utilizados na hematologia (venetoclax, midostaurina) são metabolizadas pela mesma via dos azólicos, é preciso estar atento às interações.[134]

Como alternativa aos triazólicos, as formulações lipídicas da anfotericina são opções em pacientes com toxicidade, que não estão respondendo ao tratamento ou que estavam em uso de profilaxia para fungo filamentoso.[77, 125] Os efeitos adversos mais comuns são relacionados à infusão, como febre e calafrios, nefrotoxicidade e hipocalemia.[135] Entre as formulações disponíveis, a anfotericina lipossomal na dose de 3mg/kg/dia é a droga de escolha por ter perfil de toxicidade menor.[136] Em um estudo que comparou 3mg/kg/dia com 10mg/kg/dia de anfotericina lipossomal no tratamento da aspergilose mostrou que não havia benefício em usar doses maiores e que estava associado a maior toxicidade.[137] A anfotericina deoxicolato é muito tóxica e, portanto, não deve ser usada.[123]

As equinocandinas tem eficácia limitada no tratamento da AI e não estão recomendadas como monoterapia.[138, 139] A terapia combinada não está indicada na primeira linha, porém pode ser considerada em situações como terapia de resgate em pacientes que não responderam a primeira linha, em áreas onde há altas taxas de resistência ou enquanto não souber o teste de susceptibilidade.[125]

2.6.3 Fusariose invasiva

Os antifúngicos disponíveis para tratamento da fusariose são as formulações lipídicas da anfotericina B e o voriconazol, porém sem estudo randomizado

comparando essas drogas.[140] Um estudo retrospectivo, multicêntrico com 233 pacientes diagnosticados com fusariose mostrou que a probabilidade de sobrevida em 90 dias com voriconazol, com anfotericina B lipídica e anfotericina deoxicolato foi de 60%, 53% e 28%, respectivamente (p=0,04).[83] Além disso, foram encontrados como fatores de pior prognóstico o uso de corticosteroides, neutropenia no final do tratamento e tratamento com anfotericina deoxicolato.[83] Logo, assim como em outras DFI, a formulação convencional de anfotericina não está indicada e pode piorar o quadro clínico dos pacientes devido aos efeitos colaterais.

De uma forma geral, as espécies de *Fusarium* apresentam uma concentração inibitória mínima (CIM) alta para todos os antifúngicos, sendo maior para os azólicos, não havendo ponto de corte estabelecido.[43, 141] No entanto, não há uma correlação entre CIM e desfecho clínico. Nucci e cols. mostraram que em 22 pacientes com FI tratados com voriconazol, não houve diferença com relação ao CIM nos pacientes que sobreviveram comparados aos óbitos.[141] Portanto, a identificação da espécie e os testes de susceptibilidade não devem ser utilizados para guiar o tratamento, mas sim para fins epidemiológicos.

Com base nos estudos publicados, a diretriz atual de tratamento de fungos raros recomenda voriconazol ou uma formulação lipídica de anfotericina.[43, 140] E, apesar de não existir dados mostrando que terapia combinada é melhor do que monoterapia, nesta diretriz a força da recomendação é a mesma para ambas as opções terapêuticas. É importante destacar, que, assim como em outras doenças fúngicas em pacientes hematológicos, a recuperação medular é fundamental para o sucesso terapêutico.[142]

2.6.4 Mucormicose

O sucesso no tratamento da mucormicose depende de três fatores: uso precoce de um antifúngico adequado, controle do foco infeccioso com cirurgia e, como nas outras doenças fúngicas em pacientes hematológicos, resolução da neutropenia. [143] Além disso é fundamental o controle dos fatores de risco como redução do uso de corticosteroide e correção de hiperglicemia.[143, 144]

As terapias antifúngicas recomendadas para o tratamento da mucormicose são a anfotericina lipossomal e os triazólicos isavuconazol e posaconazol, sendo este

último aprovado apenas como opção de resgate em pacientes refratários.[144-146] Apesar de estudos com modelo animal mostrarem maior eficácia no uso da terapia combinada de equinocandina com anfotericina comparado a monoterapia, os resultados em estudos clínicos foram controversos.[143, 147, 148] Portanto, na ausência de estudos prospectivos comparativos, o uso de terapia dupla não está recomendado.

Por outro lado, o controle do foco infeccioso com cirurgia está bem estabelecido. No entanto, em pacientes hematológicos, procedimentos cirúrgicos são complexos devido às citopenias graves decorrentes da doença e do tratamento.[149-151]

2.7 Profilaxia antifúngica

Os grupos de maior risco para DFI são os pacientes com leucemia aguda tratados com protocolo quimioterápico intenso e aqueles submetidos ao TCH alogênico, sendo a neutropenia grave e prolongada por mais de 7 a 10 dias o principal fator de risco para infecção por fungos filamentosos, e a mucosite para candidemia.[61] Nos pacientes com LMA, a estratificação de risco baseada em fatores do hospedeiro, da doença e do meio ambiente auxiliam a definir a melhor estratégia de profilaxia.[63] Em centros com alta incidência de infecção por fungo filamentoso, os azólicos de amplo espectro são a primeira escolha para profilaxia primária de DFI, sendo posaconazol o mais indicado com base em um estudo randomizado que mostrou redução de DFI e aumento da sobrevida quando comparado com fluconazol ou itraconazol.[152] Além disso, estudos retrospectivos confirmaram o benefício do posaconazol.[153, 154] Apesar da ausência de estudos randomizados, o voriconazol pode ser considerado uma alternativa.[155] Por um outro lado, em locais com baixa incidência de aspergilose, pode ser adotado a estratégia de fluconazol profilático e rastreio semanal com biomarcadores como a galactomanana e uso precoce de exame de imagem.[156] Um estudo que comparou terapia empírica ou preemptiva mostrou que esta última é uma opção segura mesmo com o uso da profilaxia com fluconazol em pacientes de alto risco.[157] Em pacientes com LMA tratados com protocolos menos intensos o uso da profilaxia primária é controverso e deve ser avaliado com cautela.[158] Fatores como a epidemiologia local, interação

medicamentosa com as novas drogas e toxicidade devem ser incorporados a uma estratégia baseada no risco de DFI para definir a necessidade do uso da profilaxia neste grupo de pacientes.[159-161]

No cenário do TCH alogênico, os períodos de maior risco para infecção fúngica são os primeiros 30 dias até a recuperação dos neutrófilos e após a enxertia se houver DECH com uso de corticosteroide e imunossupressores.[47] Na fase precoce do TMO, doença em atividade, infecção fúngica prévia, sobrecarga de ferro e neutropenia por mais de 3 semanas são fatores que aumentam o risco de DFI, assim como DECH aguda graus III-IV, não responsiva a corticoide e seguida de DECH crônica, aumentam o risco infecção por fungo filamentoso após a enxertia da medula.[162] Além disso, para definir qual antifúngico profilático usar, é importante que cada centro tenha seus dados epidemiológicos. Desta forma, de acordo com o consenso europeu, no período pré pega da medula, em grupos de baixo risco para infecção por fungo filamentoso, pode-se utilizar a estratégia combinada de fluconazol com biomarcadores.[163] No entanto, se a incidência é alta, estão recomendados voriconazol ou posaconazol.[163, 164] Estes últimos também estão indicados no período pós enxertia. Entre as equinocandinas, apenas a micafungina foi analisada em estudo randomizado comparada com fluconazol, sem mostrar diferença entre os dois grupos.[165, 166] Portanto, está recomendada em casos de toxicidade hepática ou em que há interação medicamentosa com os azólicos.[167]

Nos pacientes com LLA, a incidência de DFI é variável, entre 7% e 12%.[5, 168] No entanto, apesar da alta frequência, não há recomendação formal para o uso de profilaxia antifúngica principalmente pelo risco de interação medicamentosa com os alcaloides como a vincristina que está presente em muitos protocolos de tratamento da leucemia linfoblástica aguda.[169]

A incidência de DFI em pacientes submetidos ao TCH autólogo é menor quando comparada ao alogênico, sendo descrito na literatura como menor do que 2%.[170] Os indivíduos que desenvolvem mucosite, apresentam risco elevado de candidemia e, portanto, a profilaxia primária com fluconazol deve ser considerada.[167]

2.8 Uso racional de antifúngicos na hematologia

A resistência antifúngica tem emergido como um desafio crítico no manejo da DFI, especialmente com o aumento de espécies resistentes de *Candida* spp. e *Aspergillus* spp..[171, 172] A resistência a *Candida* está frequentemente associada ao uso inadequado ou excessivo de antifúngicos, tanto na profilaxia quanto no tratamento empírico.[28, 173] Além disso, fatores relacionados ao meio ambiente, como o uso de fungicidas na agricultura, tem contribuído para o aumento de espécies de *Aspergillus fumigatus* resistente aos azólicos.[174] Portanto, a monitorização contínua dos padrões de resistência local e global é essencial para prevenir a DFI, orientar a escolha terapêutica, assim como o diagnóstico rápido e preciso através de exames de imagem, biomarcadores e técnicas moleculares.[175, 176] Além disso, a prescrição inadequada de antifúngicos pode resultar no aumento da toxicidade, interações medicamentosas e elevação dos custos no sistema de saúde.[176] Uma das estratégias utilizadas para mitigar esses problemas são os programas de gerenciamento do uso de antifúngicos.[175, 177] Através deles busca-se como objetivo promover a prescrição adequada, baseando-se em evidências clínicas e microbiológicas para assegurar a eficácia do tratamento e minimizar efeitos adversos.

Portanto, a constante atualização médica no manejo da DFI é fundamental, dada a introdução de novas terapias e a evolução dos perfis de resistência dos patógenos sendo necessário estar atento as diretrizes atuais e às características farmacológicas dos antifúngicos disponíveis, incluindo espectro de ação, farmacocinética e potenciais interações medicamentosas.[171, 178] Diante da identificação de lacunas relacionadas ao conhecimento das complicações infecciosas em pacientes hematológicos, das controvérsias relacionadas ao uso de profilaxia antifúngica no TCH autólogo e em pacientes com LMA recebendo tratamentos menos intensivos, e dos desafios no diagnóstico e tratamento da fusariose invasiva, foram desenvolvidos quatro artigos que discutem esses temas.

3 OBJETIVOS

3.1 Principal

Identificar lacunas no conhecimento dos hematologistas sobre DFI, gerar evidências sobre o tema e desenvolver ferramentas que otimizem o manejo do paciente hematológico com infecção fúngica

3.2 Secundários

- Avaliar o conhecimento dos hematologistas sobre complicações infecciosas na neutropenia febril e no TCH
- Comparar duas estratégias de profilaxia com fluconazol no TCH autólogo
- Revisar a incidência e os fatores de risco para DFI em pacientes com LMA recebendo quimioterapia intensiva, monoterapia com azacitidina ou em combinação com venetoclax, discutir sobre a necessidade de profilaxia antifúngica e estratificar o risco de DFI neste grupo de pacientes
- Desenvolver uma ferramenta que avalie a adesão às diretrizes no manejo da fusariose invasiva.

4 METODOLOGIA

Foram publicados quatro artigos como produto desta tese. A metodologia de cada artigo será detalhada nos subitens a seguir. Não houve financiamento em nenhum dos estudos.

4.1 Artigo 1: “Evaluation of the knowledge of hematologists about the management of infectious complications in hematologic patients”

Neste estudo foi avaliado o nível de conhecimento de hematologistas brasileiros sobre o manejo de complicações infecciosas em pacientes hematológicos de alto risco, incluindo aqueles com neoplasias hematológicas ou submetidos a TCH. Os participantes, responderam a dois questionários *online*, cada um com 20 perguntas de múltipla escolha, desenvolvidos para avaliar conhecimentos sobre epidemiologia, profilaxia, diagnóstico e tratamento de complicações infecciosas, com foco em neutropenia febril (questionário 1) e manejo de infecções em TCH autólogo e alogênico (questionário 2). As variáveis categóricas foram expressas em números absolutos e porcentagens e comparadas utilizando os testes de Qui-quadrado ou exato de Fisher, conforme apropriado. Já as variáveis contínuas foram resumidas em medianas e intervalos e comparadas por meio dos testes de Mann-Whitney e Kruskal-Wallis. Um valor de $p < 0,05$ foi considerado estatisticamente significativo.

4.2 Artigo 2: “Early versus Late Fluconazole Prophylaxis in Autologous Hematopoietic Cell Transplantation”

Este estudo retrospectivo foi realizado no Hospital Universitário Clementino Fraga Filho, Universidade Federal do Rio de Janeiro, Brasil, um hospital terciário afiliado à universidade. A Unidade de Hematologia possui oito quartos individuais com filtragem de ar particulado de alta eficiência (HEPA) e pressão positiva, e cinco quartos duplos sem filtragem HEPA. O estudo foi aprovado pelo Comitê de Ética do hospital (Estudo 077-16).

Neste estudo retrospectivo foram revisados os episódios de neutropenia febril em pacientes submetidos a TCH autólogo entre 1997 e 2017 para tratamento de neoplasias hematológicas. De 1997 a 2003, a profilaxia antifúngica com fluconazol (400 mg/dia) era iniciada precocemente, durante o regime de condicionamento, e mantida até a recuperação neutrofílica ou necessidade de terapia antifúngica não profilática. A partir de 2004, o fluconazol passou a ser administrado apenas em casos de mucosite (profilaxia guiada). Dados como características clínicas, regime de condicionamento, duração da neutropenia, classificação dos episódios febris, ocorrência de DFI e desfechos foram analisados. A hipótese testada foi que a profilaxia tardia seria tão eficaz quanto a precoce, comparando-se três grupos: profilaxia precoce, tardia e sem profilaxia. As análises estatísticas foram realizadas com testes de Qui-quadrado, Fisher e Kruskal-Wallis.

4.3 Artigo 3: “Should patients with acute myeloid leukemia treated with venetoclax-based regimens receive antifungal prophylaxis?”

Foi realizada uma revisão de todos os artigos publicados sobre a epidemiologia da DFI em pacientes com LMA tratados com protocolos menos intensos e proposto uma nova estratificação de risco de DFI neste grupo de pacientes.

4.4 Artigo 4: “EQUAL Fusariosis score 2021: An European Confederation of Medical Mycology score derived from current guidelines to measure QUALity of the clinical management of invasive fusariosis”

Neste estudo, revisamos as diretrizes da Sociedade Europeia de Microbiologia Clínica e Doenças Infecciosas (ESCMID) e da Confederação Europeia de Micologia Médica (ECMM), e selecionamos as recomendações mais robustas para o manejo dos pacientes com fusariose. As recomendações foram agrupadas em profilaxia, diagnóstico, tratamento e acompanhamento, com foco nas recomendações de nível "A" a "C" para um manejo ideal. A seção de diagnóstico recebeu maior peso devido à sua importância para o prognóstico, sendo subdividida em exames de imagem, exame direto e cultura de sangue e lesões cutâneas, histopatologia, testes sorológicos, identificação de espécies e testes de susceptibilidade. A seção de tratamento incluiu opções de primeira linha, terapias adjuvantes, desbridamento cirúrgico, transfusão de granulócitos e uso de fatores estimulantes de colônias. Já o acompanhamento foi baseado no monitoramento da resposta ao tratamento por meio do teste de galactomanana sérica.

5 RESULTADOS

Os resultados desta tese foram divididos em quatro artigos publicados que estão descritos a seguir.

5.1 Artigo 1: “Evaluation of the knowledge of hematologists about the management of infectious complications in hematologic patients”

O estudo analisou 289 respostas no total. A maioria dos participantes era de médicos da região sudeste do Brasil e trabalham em ambos os sistemas público e privado de saúde. A pontuação mediana foi 5,0 em ambas as pesquisas.

No questionário 1, sobre neutropenia febril, destacou-se o baixo conhecimento sobre ajuste de dose de cefepima (8% de acertos) e a indicação de profilaxia secundária para candidemia (16% de acertos). Por outro lado, as questões com maiores números de acerto foram aquelas sobre os principais agentes de bacteremia por Gram-negativos (82%) e sobre o manejo de candidemia em pacientes com hemocultura positiva (80%). Os hematologistas que trabalham com TCH assim como clínicos mais jovens (menos de 40 anos) foram aqueles com pontuações mais altas.

No questionário 2, sobre complicações infecciosas no TCH, as questões com menor acerto foram sobre manejo de infecção por citomegalovírus e do isavuconazole como uma alternativa de tratamento da mucormicose. Assim como no questionário 1, médicos hematologistas que atuam com TCH tiveram melhor desempenho em questões sobre infecções virais e fúngicas, com pontuação mediana de 6,0, comparado a 4,5 para os que tratam apenas neoplasias hematológicas. Não houve diferença significativa entre categorias profissionais (médicos, residentes e professores), mas quando analisado algumas questões de forma individual, professores acertaram mais em questões específicas, como culturas positivas para *C. krusei*. A idade não influenciou significativamente os resultados.

5.2 Artigo 2: “Early versus Late Fluconazole Prophylaxis in Autologous Hematopoietic Cell Transplantation”

Durante o período do estudo, foram realizados 583 TCHs autólogo em pacientes com neoplasias hematológicas. Foram excluídos 12 pacientes que receberam outros

regimes de profilaxia (itraconazol, voriconazol ou posaconazol), sendo então analisado 571 TCHs em 559 pacientes, dos quais a idade mediana foi de 49 anos e 56,2% eram homens. As doenças de base mais frequentes foram mieloma múltiplo (54,1%), linfoma de Hodgkin (24,0%) e linfoma não Hodgkin (18,2%). A profilaxia com quinolona foi usada em 44,6% dos casos, e a profilaxia com fluconazol em 66,9% (270 precoce e 112 com tardia). O esquema antibiótico mais comum na neutropenia febril foi a monoterapia com cefepima (83% dos episódios). A terapia antifúngica não profilática foi necessária em 8,9% dos casos, principalmente para terapia empírica, candidíase oral ou DFI. A duração mediana da neutropenia foi de 8 dias, e a mortalidade geral foi de 5,4%. DFI foi diagnosticada em 3,3% dos TCH, incluindo 7 episódios de candidemia.

Foram comparados os três grupos de profilaxia (precoce, tardia e sem profilaxia), e, como esperado, a mucosite oral foi menos frequente no grupo que não recebeu profilaxia (39,2%) em comparação com os grupos de profilaxia precoce (66,5%) e tardia (79,5%). A duração mediana da profilaxia com fluconazol foi de 17 dias no grupo de profilaxia precoce e 6 dias no grupo de profilaxia tardia. Candidemia ocorreu em 1,8% dos casos no grupo de profilaxia precoce, em nenhum caso no grupo de profilaxia tardia e em 1,1% no grupo sem profilaxia, sem diferença estatisticamente significativa. Não houve diferenças na taxa de mortalidade entre os três grupos.

5.3 Artigo 3: “Should patients with acute myeloid leukemia treated with venetoclax-based regimens receive antifungal prophylaxis?”

Neste artigo revisamos na literatura os fatores de risco para DFI em pacientes com LMA tratados com protocolos intensos, com hipometilantes e com esquemas baseados no uso de venetoclax. Além disso, exploramos os problemas relacionados ao uso de antifúngicos como toxicidade e interação medicamentosa.

Com base nos dados encontrados, discutimos que a profilaxia antifúngica não deve ser aplicada de forma universal a todos os pacientes com LMA tratados com regimes baseados em venetoclax. Portanto, sugerimos uma estratégia de estratificação de risco considerando fatores como quimioterapia prévia, neutropenia

no início do ciclo, grupo de risco da LMA, probabilidade de resposta completa, LMA recidivada/refratária, LMA secundária ou relacionada a terapia, mutação TP53 e condições clínicas do paciente. Além disso, aspectos epidemiológicos locais e fatores de risco previamente estabelecidos para DFI (uso de corticosteroides, comorbidades, exposição ambiental) devem ser considerados.

5.4 Artigo 4: "EQUAL Fusariosis score 2021: An European Confederation of Medical Mycology score derived from current guidelines to measure QUALity of the clinical management of invasive fusariosis"

Na criação da ferramenta EQUAL para avaliar a aderência as diretrizes para manejo dos pacientes com fusariose foram atribuídos pontos para cada recomendação. Pacientes neutropênicos ou receptores de TCH com cultura positiva para *Fusarium* em lesões cutâneas superficiais, recomenda-se profilaxia ativa com voriconazol ou posaconazol (1 ponto). Nos pacientes com histórico de fusariose invasiva que serão submetidos a novos períodos de imunossupressão devem receber profilaxia secundária com voriconazol, posaconazol ou formulações lipídicas de anfotericina B (1 ponto). Na presença de febre persistente ou recorrente, apesar do uso de antibióticos de amplo espectro, deve-se coletar hemocultura (2 pontos) e solicitar tomografia computadorizada de tórax e seios da face (2 pontos). Lesões cutâneas (pápulas ou nódulos eritematosos com necrose central) exigem biópsia, com exame microscópico direto (2 pontos) para diagnóstico presuntivo rápido. Cultura (2 pontos) e histopatologia (2 pontos) de tecidos também são fortemente recomendados. Testes sorológicos, como galactomanana (1 ponto) e 1,3-beta-D-glucano (1 ponto), podem ser úteis antes do surgimento de manifestações clínicas. A identificação de espécies por MALDI-TOF ou RCP (1 ponto) e testes de susceptibilidade antifúngica (1 ponto) têm relevância epidemiológica, mas não são essenciais para o tratamento. Com relação ao tratamento, a primeira linha inclui formulações lipídicas de anfotericina B ou voriconazol (2 pontos), com a opção de terapia combinada (voriconazol + anfotericina B lipídica) (2 pontos). Em casos de infecção local com tecido necrótico, o desbridamento cirúrgico é recomendado (2

pontos). Medidas adjuvantes, como fatores estimulantes de colônias (G-CSF ou GM-CSF) e transfusão de granulócitos (1 ponto), podem ser utilizadas para tentar auxiliar na recuperação dos neutrófilos. Se ao diagnóstico, a galactomanana era positiva, recomenda-se o monitoramento (2 pontos). Essas recomendações visam otimizar o manejo da fusariose invasiva, considerando aspectos clínicos, diagnósticos e terapêuticos.

6 DISCUSSÃO

A DFI é uma complicação frequente e grave que tem impacto negativo na sobrevida dos pacientes hematológicos.[3, 4] Nos quatro artigos publicados foram discutidos pontos relevantes como: (1) a importância do conhecimento sobre as infecções bacteriana, fúngicas e virais no manejo adequado dos pacientes, (2) o desafio da atualização médica constante, (3) estratégias de profilaxia antifúngica e uma nova estratificação de risco de DFI em pacientes com LMA, (4) o uso racional de antifúngicos com o objetivo de reduzir resistência, toxicidade e interação medicamentosa e, (5) aderência as diretrizes como forma de melhorar o diagnóstico e tratamento da DFI.[179-182]

Diferentes estudos já utilizaram questionários para avaliar o nível de conhecimento dos médicos em diferentes cenários.[183, 184] Na hematologia, o foco tem sido identificar as práticas de manejo de pacientes hematológicos adultos e pediátricos, e não a avaliação do conhecimento específico sobre determinado tema. [183, 185] Ao utilizar dois questionários com perguntas direcionadas para diferentes temas relacionados a infecção em pacientes hematológicos, identificamos as lacunas no conhecimento dos hematologistas sobre o diagnóstico, tratamento e profilaxia das infecções. Com base nos achados do estudo, foi possível evidenciar a importância de desenvolver atividades de educação continuada com foco no manejo das infecções fúngicas invasivas em pacientes hematológicos, por meio de cursos de atualização online, simulações clínicas interativas, revisões de casos guiadas por especialistas e cursos multidisciplinares nos centros que integrem hematologistas e

infectologistas visando à implementação de protocolos baseados em evidências e à melhoria dos desfechos clínico.

Com relação ao uso da profilaxia antifúngica, questionamos o uso de fluconazol no TCH autólogo e em pacientes com LMA tratados com protocolos de baixa intensidade.[182] O uso de antifúngico profilático no TCH autólogo é realizado de forma rotineira em muitos centros sem utilizar uma avaliação de risco guiada pela presença de mucosite, principal fator de risco para candidemia.[186, 187] Por isso, ao comparar duas estratégias de profilaxia (precoce e tardia), mostramos que: a incidência de candidemia não foi diferente entre os grupos que receberam profilaxia precoce ou tardia com fluconazol, a duração média do uso de fluconazol foi significativamente menor no grupo de profilaxia tardia, e que a DFI é infrequente no transplante autólogo. Portanto, o uso do fluconazol guiado pela presença da mucosite reduz o uso desnecessário de antifúngicos e pode minimizar o risco de resistência fúngica. Da mesma forma, diferente da estratificação de risco de DFI em pacientes com LMA recebendo tratamento intensos que já existe, não há até o momento uma discussão sobre profilaxia antifúngica com protocolos menos intensos usando venetoclax e hipometilantes o que culmina com a prescrição universal de antifúngico.[63] Considerando que a epidemiologia da DFI neste grupo de pacientes é heterogênea e que os fatores de risco podem ser diferentes daqueles tratados com protocolos intensos, foi realizado uma revisão sobre com o tema e proposto uma nova estratificação de risco de DFI baseada nas características do hospedeiro, da doença e do meio ambiente.[180] Ao questionar o uso universal da profilaxia, abordamos os possíveis problemas relacionados ao uso contínuo de antifúngicos como interações medicamentosas, toxicidade e aumento de resistência fúngica e sugerimos estratificar em dois grupos de risco para DFI, baixo e alto, que auxiliam na decisão de iniciar profilaxia na beira do leito. Ambos os estudos, reforçam a importância de avaliar individualmente o risco de DFI e adaptar as estratégias de profilaxia conforme o contexto clínico com o objetivo de usar racionalmente os antifúngicos.

Por fim, criamos o "EQUAL Fusariosis score”, uma ferramenta útil para avaliar a qualidade do manejo da fusariose invasiva que é uma DFI prevalente no Brasil comparada a outras regiões, tem alta mortalidade e de difícil tratamento.[14, 55] Com base nas diretrizes das sociedades europeias de micologia, o artigo enfatiza a

importância do diagnóstico precoce e preciso, além do tratamento adequado, para melhorar os desfechos dos pacientes.[53, 140] A fusariose, assim como outras DFI, requer um alto índice de suspeição clínica e o uso de métodos diagnósticos avançados, como biomarcadores e técnicas moleculares.[140] A implementação do "EQUAL Fusariosis Score" pode ajudar a padronizar práticas clínicas, garantindo que os pacientes recebam o manejo mais adequado, baseado em evidências.[179] Outras ferramentas como esta também foram desenvolvidas para avaliar o manejo de candidemia, aspergilose invasiva, mucormicose e criptococose e estão disponíveis em diferentes idiomas.[188-191]

7 CONCLUSÃO

1) **Avaliar o conhecimento dos hematologistas sobre complicações infecciosas na neutropenia febril e no TCH**

   A pontuação baixa na avaliação do conhecimento sobre DFI mostra a necessidade de atualização médica em DFI e uma oportunidade para iniciar programas de educação continuada (hematologia e infectologia).

2) **Comparar duas estratégias de profilaxia com fluconazol no TCH autólogo**

   O uso racional de antifúngicos reduz resistência, toxicidade e o risco de interação medicamentosa sem comprometer a mortalidade no TCH autólogo.

3) **Revisar a incidência e os fatores de risco para DFI em pacientes com LMA recebendo quimioterapia intensiva, monoterapia com azacitidina ou em combinação com venetoclax, discutir sobre a necessidade de profilaxia antifúngica e estratificar o risco de DFI neste grupo de pacientes**

Em pacientes com LMA tratados com venetoclax é necessário adequar as estratégias de profilaxia antifúngica através de uma nova estratificação de risco de DFI

4) **Desenvolver uma ferramenta que avalie a adesão às diretrizes no manejo da fusariose invasiva.**

A adesão as diretrizes é uma forma de otimizar diagnóstico e tratamento da fusariose invasiva.

A utilização de ferramentas que auxiliem no diagnóstico da DFI pode ter impacto na mortalidade dos pacientes

Em síntese, esses quatro artigos destacam a conexão entre o conhecimento sobre DFI, o uso racional de antifúngicos, a profilaxia individualizada e o diagnóstico preciso. A educação continuada com atualizações constantes, a adoção de estratégias de profilaxia baseadas em risco e a implementação de ferramentas de avaliação da qualidade do manejo são essenciais para otimizar o cuidado de pacientes hematológicos em risco de DFI e reduzir a morbimortalidade associada a essas infecções. Além disso, esses estudos são a base para o desenvolvimento de projetos no futuro como a validação do escore de risco de DFI em pacientes com LMA tratados com venetoclax, avaliação na prática da aderência as diretrizes de fusariose utilizando o “EQUAL” e promover atividades de educação continuada sobre DFI.

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APÊNDICE

Artigo 1: “Evaluation of the knowledge of hematologists about the management of infectious complications in hematologic patients”

HEMATOL TRANSFUS CELL THER. 2024;46(2):125–130

HEMATOLOGY, TRANSFUSION AND CELL THERAPY

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Original article

Evaluation of the knowledge of hematologists about the management of infectious complications in hematologic patients

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ARTICLE INFO

Article history:
Received 13 July 2022
Accepted 11 January 2023
Available online 9 February 2023

Keywords:
Febrile neutropenia
Hematopoietic cell transplantation
Survey
Education

ABSTRACT

Introduction: Infection is a serious complication among patients with hematologic malignancies (HMs) and in hematopoietic cell transplant (HCT) recipients. In most centers, the management of these complications is provided by the hematologist in person, thus demanding a knowledge of basic aspects of infection.

Methods: To evaluate the knowledge of the hematologist on infections, we invited clinicians to answer two questionnaires with 20 multiple-choice questions covering epidemiology, prophylaxis, diagnosis and treatment of infection in patients with HMs and HCT.

Results: We obtained 289 answers: 223 in survey 1 (febrile neutropenia) and 66 in survey 2 (infection in HCT). The median score was 5.0 in both surveys (range 0.5 - 9.0). In survey 1, the questions with the lowest number of correct answers were Q3 (8%), concerning the cefepime dose, and Q1 (9%), which asked about the epidemiologic link between the use of high dose cytarabine and viridans streptococcal bacteremia. In survey 2, two questions about cytomegalovirus (CMV) infection had the lowest percentage of correct answers (Q4, 12% and Q11, 18%). Clinicians attending to HCT recipients had higher scores, compared to clinicians attending to patients with HM only (median score of 5.0 and 4.5, $p = 0.03$, in survey 1 and 6.0 and 4.5, $p = 0.001$, in survey 2). In both surveys staff clinicians, residents and professors had similar scores.

Conclusion: This is the first study in Brazil assessing the knowledge of hematologists on infectious complications. The low median score overall indicates an urgent need for continuous education. Such initiatives will eventually result in better patient care.

Introduction

Infection is a major complication in patients with hematologic malignancies (HMs) receiving intensive chemotherapy or hematopoietic cell transplantation (HCT), with high morbidity and mortality rates.[1,2] Infection in this scenario may be caused by bacteria, fungi, viruses and parasites, with clinical

This study was presented in part at the European Hematology Association (EHA) Congress 2022 in June, Vienna, Austria.

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https://doi.org/10.1016/j.htct.2023.01.003

manifestations that are usually non-specific. At most centers, the management of infectious complications is provided by the hematologist in person, thus demanding a knowledge of basic aspects of infection. However, hematologists are already overwhelmed by the large amount of new information regarding the management of the underlying hematologic disease. On the other hand, major advances in the management of infectious diseases have occurred, including improvements in culture and identification of microorganisms,[3,4] new biomarkers and diagnostic tools,[5] new antimicrobial drugs,[6] concepts of pharmacokinetics and pharmacodynamics of antimicrobial agents[7] and therapeutic drug monitoring,[8] among others. Therefore, managing infection in hematologic patients represents a great challenge.

One of the most important activities to improve the quality of patient care is education. However, to promote adequate educational programs, it is important to know possible gaps in the knowledge of different aspects of infection to develop targeted educational activities. With this aim, we performed a web-based survey with two questionnaires to evaluate the level of knowledge of the hematology community on infectious complications in febrile neutropenia and HCT.

Materials and methods

Study population

We invited clinicians from different parts of Brazil to answer a survey to evaluate the level of knowledge on the management of infectious complications in high-risk hematologic patients. The clinicians had to have experience in treating patients with hematologic malignancies and/or patients undergoing HCT. The recruiting of responders was performed by an announcement in the ABHH ("Associação Brasileira de Hematologia e Hemoterapia" – Brazilian Society of Hematology and Blood Transfusions) website. The participation in the survey was voluntary and anonymous and included hematologists from public and private centers.

Survey

Two questionnaires were developed, both with 20 multiple-choice questions covering areas of the epidemiology, prophylaxis, diagnosis and treatment of infectious complications in hematologic patients. The first questionnaire (survey 1) was intended to evaluate the knowledge of hematologists in the management of febrile neutropenia. This included the most frequent pathogens causing infection and the recognition of clinical syndromes and strategies of antibiotic and antifungal prophylaxis and treatment. The second questionnaire (survey 2) covered topics related to the management of infectious complications in autologous and allogeneic HCT. The questions were built by one of the authors (M.N.) and the selection of the correct answers was made by the same author, based on his personal experience. We also collected basic sociodemographic data on hematologists, such as age, gender, region, hospital type (public or private), clinician category (resident, staff clinician or professor) and the main area of clinical practice (HM or HCT). Each correct answer was scored as 0.5, up to the maximum score of 10 points. The full survey instrument is available in Supplementary files 1 and 2. The questionnaires were provided to hematologists as an online tool, using the Survey Monkey platform.

Statistical analysis

We calculated the median score obtained by each participant and compared scores according to the main area of clinical practice, clinician category and age group (< 30 years, 31 - 40, 41 - 50, 51 - 60 or > 61 years old). Categorical variables were expressed as absolute numbers and percentage and were compared using Chi-square or Fisher's exact test, as appropriate. Continuous variables were summarized as medians and ranges and compared using the Mann-Whitney and the Kruskal-Wallis test. A p-value < 0.05 was considered statistically significant. Database creation and statistical analyses were performed using the SPSS version 21.0 (IBM, Armonk, NY, USA). This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

Results

During the study period, we obtained 289 answers: 223 in survey 1 and 66 in survey 2. Demographic characteristics of participants are summarized in Table 1. The median age of participants in surveys 1 and 2 was 38 (range 23 - 68) and 36 (range 26 - 63), respectively. Most clinicians were staff physicians working with HM in both public and private hospitals. The majority of respondents were from the southeast region of Brazil. Overall, the median score was 5.0 in both surveys (range 0.5 - 9.0).

Survey 1: *febrile neutropenia*

Overall, seven out of the 20 questions evaluated the knowledge of clinicians regarding the epidemiology, diagnosis and management of bacterial infections and 13 focused on invasive fungal diseases (IFDs). Among the seven questions dealing with bacterial disease, the lowest percentage of correct answers (8%) was question Q3. The question asked if cefepime should be given at a fixed dose and schedule or if the dose should be individualized, based on body weight and creatinine clearance. The second question with a low percentage of correct answers (9%) was question Q1, which asked about the epidemiologic link between the use of high-dose cytarabine and viridans streptococcal bacteremia.

Concerning IFDs, question Q20 had the lowest percentage of correct answers (16%). In this question, we asked if secondary prophylaxis was indicated for patients with a previous episode of candidemia. Most of the hematologists (83%) answered that secondary prophylaxis with fluconazole was needed. The question with the highest percentage of correct answers was Q7; 82% of clinicians answered that *Pseudomonas aeruginosa*, *Klebsiella sp.* e *Escherichia coli* are the leading agents of Gram-negative bacteremia in febrile neutropenia. The second questions with the highest percentage of correct answers (80%) tested the skills of clinicians in the management of

Table 1 – Demographic characteristics of participants.

Characteristic	Survey 1 $n = 223$	Survey 2 $n = 66$
Median age (range)	38 (23 – 68)	36 (26 - 63)
Gender (male:female)	91:132	26:40
Physician category*		
Resident	39 (17)	17 (26)
Staff	151 (68)	39 (59)
Professor	14 (6)	9 (14)
Type of patient attended to by physician		
Hematologic malignancy	145 (65)	31 (47)
Hematopoietic cell transplantation	23 (10)	13 (20)
Both	55 (25)	22 (33)
Type of hospital**		
Public	75 (34)	25 (38)
Private	39 (17)	10 (15)
Both	109 (49)	30 (45)
Region***		
Southeast	134 (60)	47 (71)
South	31 (14)	4 (6)
Northeast	23 (10)	1 (2)
Midwest	15 (7)	–
North	5 (2)	1 (2)

Numbers in parentheses represent percentages unless specified.

* Missing data in 19 participants in survey 1 and one in survey 2.
** Missing data in 1 participant in survey 2.
*** Missing data in 15 participants in survey 1 and 13 in survey 2.

patients with a positive blood culture for yeast (Q18) and Q14 (primary therapy for invasive aspergillosis).

Overall, staff clinicians (4.5, range 0.5 - 9.0), residents (5.0, range 2.0 - 8.0) and professors had similar scores (4.0, range 1.5 - 7.5, $p = 0.56$). On the other hand, when we analyzed individual questions, some differences were observed. In Q12 (discontinuation of antibiotics after engraftment in autologous HCT) the rates of correct answers were 56%, 32% and 21% for residents, staff clinicians and professors, respectively ($p = 0.009$). Likewise, in Q5 (knowledge on characteristics of different antifungal agents), staff clinicians had the highest rates of correct answers (51%, compared to 47% for residents and only 14% for professors, $p = 0.02$) (Table 2).

The median scores of clinicians attending to HCT recipients were higher, compared to clinicians attending to patients with HM only (5.0, range 1.5 – 7.0 vs. 4.5, range 0.5 – 9.0, respectively, $p = 0.03$). As shown in Table 2, in four questions, clinicians attending to HCT recipients had significantly higher percentages of correct answers, compared to clinicians attending to HM only: question Q8, testing knowledge on amphotericin B (60% vs. 46%, $p = 0.04$); question Q10, which asked about the management of fever, skin rash and dyspnea in autologous HCT (67% vs. 49%, $p = 0.01$); question Q14 (primary therapy of invasive aspergillosis, 88% vs. 75%, $p = 0.02$), and; question Q15 (skin nodules representing the first clinical manifestation of invasive fusariosis (78% vs. 65%, $p = 0.05$).

We also observed a significant difference in the median scores by age group: 5.0 (range 2.0 - 8.0) for clinicians < 30 years old, 5.0 (range 1.5 - 9.0) for those between 31 and 40 years old, 4.5 (range 0.5 - 8.0) for those between 41 and 50 years, 4.0 (range 1.5 - 7.5) for those between 51 and 60 years and 3.0 (range 1.5 - 6.5) for clinicians > 60 years old ($p < 0.001$).

Survey 2: infectious complications in HCT

The 20 questions of survey 2 covered topics on bacterial (6 questions), fungal (7 questions) and viral (7 questions) infections. As shown in Table 3, among the three questions with the lowest percentages of correct answers, two tested the knowledge of clinicians on the management of cytomegalovirus (CMV) infection in HCT (Q4, 12% and Q11, 18%), the third being on the treatment of IFDs (Q18, 17%), and most respondents did not know that isavuconazole is an option for the primary treatment of mucormycosis. On the other hand, questions on the correct diagnosis of bacterial infections and antibiotic use had the highest percentages of correct answers: 80% in Q19 (proper diagnosis and management of neutropenic enterocolitis), 79% in Q8 (no activity of meropenem against methicillin-resistant *Staphylococcus aureus*) and 77% in Q10 (engraftment syndrome post autologous HCT).

When we analyzed the scores across different groups, no statistically significant difference was observed, when comparing staff clinicians, residents and professors (5.0, range 0.5 - 9.0, 5.0, range 3.0 - 6.5, and 4.5, range 3.5 - 8.5, respectively, $p = 0.93$). However, looking at individual questions, some differences were observed (Table 3). In Q2 (positive blood culture for *C. krusei*), all nine professors answered correctly, compared to 47% of staff clinicians and 35% of residents (18%, $p = 0.005$).

Comparing clinicians working with HCT or HM only, the median scores were 6.0 (range 3.5 – 9.0) and 4.5 (range 0.5 – 9.0), respectively ($p = 0.002$). In three questions regarding viral

Table 2 – Percentage of correct answers in survey 1 (febrile neutropenia) regarding physician category and main area of clinical practice.

		Physician category				Area of clinical practice		
Question	Overall	Resident	Staff	Professor	P-value	HM	HCT or both	P-value
Q1	9	5	11	14	0.47	10	9	0.87
Q2	51	64	48	43	0.16	48	56	0.25
Q3	8	13	7	0	0.23	8	8	0.98
Q4	71	59	75	64	0.10	72	70	0.85
Q5	46	41	51	14	0.02	47	44	0.64
Q6	37	54	34	36	0.07	34	42	0.21
Q7	82	85	81	79	0.85	82	82	1.00
Q8	51	49	50	71	0.28	46	60	0.04
Q9	24	28	23	36	0.51	22	28	0.31
Q10	55	64	54	50	0.46	49	67	0.01
Q11	68	79	66	57	0.17	65	72	0.34
Q12	35	56	32	21	0.009	31	42	0.09
Q13	21	10	23	14	0.17	18	26	0.17
Q14	80	87	79	71	0.36	75	88	0.02
Q15	70	69	69	79	0.75	65	78	0.05
Q16	57	61	58	50	0.75	56	59	0.65
Q17	39	13	45	43	0.01	37	41	0.58
Q18	80	77	80	86	0.77	83	76	0.20
Q19	39	33	42	36	0.55	39	40	0.95
Q20	16	8	19	14	0.22	17	14	0.54

HM = hematologic malignancy; HCT = hematopoietic cell transplantation.

infections, clinicians working with HCT had higher scores. These questions were Q6 (herpes zoster as the most frequent viral infection in the post-engraftment period of autologous HCT, 66% vs. 26%, $p = 0.001$), Q9 (risk factors for EBV reactivation, 80% vs. 58%, $p = 0.05$) and Q20 (respiratory viruses in allogeneic HCT, 83% vs. 52%, $p = 0.007$). Other questions with significant differences were Q13 (positive blood culture for a mold, 71% vs. 39%, $p = 0.008$), Q3 (risk factor for invasive aspergillosis after HCT, 51% vs. 26%, $p = 0.03$) and Q5 (causes of diffuse infiltrates in allogeneic HCT, 57% vs. 29%, $p = 0.02$).

Table 3 – Percentage of correct answers in survey 2 (infection in hematopoietic cell transplantation) regarding physician category and main area of clinical practice.

		Physician category				Area of clinical practice		
Question	Overall $n = 66$	Resident $n = 17$	Staff $n = 40$	Professor $n = 9$	P-value	HM $n = 31$	HCT or both $n = 35$	P-value
Q1	71	71	72	67	0.94	68	74	0.56
Q2	51	35	47	100	0.005	48	54	0.63
Q3	39	29	40	56	0.43	26	51	0.03
Q4	12	23	10	0	0.17	16	9	0.35
Q5	44	29	45	67	0.19	29	57	0.02
Q6	47	35	52	44	0.49	26	66	0.001
Q7	41	29	50	32	0.17	35	46	0.40
Q8	79	88	75	78	0.53	71	86	0.14
Q9	70	59	72	78	0.50	58	80	0.05
Q10	77	88	75	67	0.39	71	83	0.25
Q11	18	12	20	22	0.72	16	20	0.68
Q12	68	82	62	67	0.34	68	69	0.94
Q13	56	53	52	78	0.37	39	71	0.008
Q14	51	41	60	33	0.21	48	54	0.63
Q15	64	65	62	67	0.97	52	74	0.06
Q16	38	41	40	22	0.58	26	49	0.06
Q17	36	65	27	22	0.02	32	40	0.51
Q18	17	12	15	33	0.34	19	14	0.58
Q19	80	82	80	78	0.96	77	83	0.58
Q20	68	59	72	67	0.59	52	83	0.007

HM = hematologic malignancy; HCT = hematopoietic cell transplantation.

Analyzing age groups, the median scores were: 5.0 (range 3.0 - 6.5) for those aged ≤ 30 years, 5.5 (range 1.0 - 9.0) for those between 31 and 40 years, 5.0 (0.5 - 8.5) for those between 41 and 50 years, 5.5 (range 2.5 - 7.5) for those between 51 and 60 years and 5.0 (range 4.5 - 5.5) for clinicians > 60 years old, $p = 0.68$.

Discussion

In the present study, we observed that hematologists with daily practice in managing febrile neutropenia and infection in HCT had a low overall score, reflecting the urgent need for continuous education. In general, we identified gaps in the management of all types of infection (bacterial, fungal and viral), with wrong answers in diagnosis, treatment and prophylaxis.

Other studies have addressed the use of surveys to evaluate the level of the physician knowledge in different scenarios.[9–12] This type of study is of great importance to identify gaps in the knowledge, helping to tailor educational activities to a certain community of physicians. Regarding infection in hematology, two studies used surveys to evaluate the practices of antimicrobial management in adults and children.[13,14]

Our study focused only on hematologists working with HM and HCT, yielding several findings regarding gaps in the knowledge of infectious complications. In survey 1, we observed that most clinicians did not know that the dose of betalactam antibiotics should be calculated on the basis of weight and creatinine clearance (Q3).[15] In this regard, the use of a fixed dose may result in overexposure to the antibiotics, increasing the risks of adverse events, or underexposure, resulting in poor response to infection. We also noted a gap in the knowledge regarding the epidemiology of bacterial infections, as most clinicians were not aware that patients receiving high doses of cytarabine are at higher risk of developing viridans streptococci bacteremia. These bacteria are colonizers of the oral cavity and the presence of mucositis induced by high-dose cytarabine increases the risk of bloodstream infection by this pathogen.[16,17]

We also observed that clinicians had the mistaken idea that secondary antifungal prophylaxis is needed in all IFDs. The majority answered that secondary prophylaxis is indicated for patients with a previous episode of candidemia, when in fact, there is no data to indicate that secondary prophylaxis is needed.[18] On the other hand, 80% of clinicians were aware that a positive blood culture for yeast in a patient with febrile neutropenia should prompt the immediate initiation of appropriate antifungal therapy.

In survey 2, the questions with the lowest rate of correct answers were on CMV infection, which might reflect the heterogeneity in current clinical practices across different institutions. In Q4, almost 30% of clinicians did not know that ganciclovir increases the risk of bacterial and fungal infection[19] and 43% did not know that acyclovir at high doses may prevent CMV infection.[20] Another aspect that deserves attention is the CMV surveillance in allogeneic HCT, as only 18% answered question Q11 correctly. The CMV surveillance after allogeneic HCT should be performed weekly, at least until day +100, and should be extended beyond day +100 in patients with graft-versus-host disease. Our survey also identified a gap in knowledge on new drugs to treat IFDs (Q7 and Q18). Isavuconazole is a broad-spectrum azole approved as primary therapy for both invasive aspergillosis and mucormycosis.[21]

Finally, we found some differences in knowledge when we analyzed scores across groups. In both surveys, although we did not find a statistically significant difference in overall scores between staff clinicians, residents and professors, we observed that in individual questions, staff clinicians seemed to have more experience than residents and professors. This might be explained by the fact that staff clinicians attend to a larger number of patients, which gives them more expertise. Furthermore, as we expected, hematologists working in both areas (HCT and HM) had the highest score. In addition, if we look into individual questions, hematologists working with HCT had the highest percentage of adequate answer regarding viral infections, probably because CMV and EBV infections are more common in this setting. Age groups were also analyzed and, in survey 1, we observed that clinicians < 40 years of age had the highest scores, probably reflecting the fact that younger hematologists, having graduated recently, may be more updated with new information.

In our survey, the questions and the selection of the correct answers were made by one of the authors, based on his personal experience in managing infection in hematologic patients in Brazil over 30 years. This likely reduced potential influences of local epidemiologic differences on the selection of correct answers by the participants.

A major limitation of our study is that since the participation was voluntary, clinicians with less expertise could have declined the invitation. In this regard, it is possible that the overall score could be even lower if there was no selection bias. Moreover, we did not have the information about the number of years of experience of clinicians in treating patients with HM and/or undergoing HCT.

Conclusion

In conclusion, our study allowed us to identify important gaps in the knowledge of Brazilian hematologists regarding the management of infectious complications in patients undergoing chemotherapy or HCT. These data indicate that there is an urgent need for continuous medical education in the field, as well as guidance for management of infection which takes into account local epidemiologic aspects. In this regard, the development of Brazilian guideline for the management of febrile neutropenia and the creation of an educational program addressing the management of infection in hematologic patients may improve clinician knowledge and patient care.

Conflicts of interest

None.

Supplementary materials

Supplementary material associated with this article can be found in the online version at doi:10.1016/j.htct.2023.01.003.

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Supplementary file 1: Febrile neutropenia questionnaire

1. A patient developed febrile neutropenia after having received high-dose cytarabine. The microbiology laboratory informs that a Gram-positive organism is growing from blood cultures. What is the most likely microorganism?

a) *Staphylococcus aureus*

b) *Streptococcus pneumoniae*

c) *Streptococcus mitis*

d) *Enterococcus faecalis*

e) *Staphylococcus epidermidis*

Correct answer: C

The most frequent Gram-positive bacteria causing bloodstream infection in febrile neutropenic patients are coagulase-negative staphylococci, *Staphylococcus aureus* and viridans streptococci (including *Streptococcus mitis*). The latter organisms colonize the oral cavity and patients with oral mucositis are at increased risk of bacteremia due to viridans streptococci.[1]

2. A patient presents relapse of acute myeloid leukemia 6 months after having obtained complete remission with a “7+3” induction regimen and 2 cycles of consolidation with high-dose cytarabine. Treatment of relapse with FLAG-Ida (fludarabine, cytarabine, filgrastim and idarubicin) is planned. Which prophylactic regimen is more important in this context?

a) Sulfamethoxazole-trimethoprim

b) Acyclovir

c) Ciprofloxacin

d) Posaconazole

e) Ivermectin

Correct answer: D

Patients with acute myeloid leukemia are at high risk for invasive fungal disease,[2] and posaconazole is the agent of choice.[3] Prophylaxis for *Pneumocystis jirovecii* pneumonia is usually not recommended in patients with acute myeloid leukemia.[4] The use of a quinolone is optional. Regarding acyclovir, reactivation of herpes simplex is less relevant than the development of an invasive fungal disease. Routine prophylaxis for strongyloidiasis is not supported by randomized studies.[5]

3. Your patient develops febrile neutropenia and you prescribe cefepime. What dose and schedule do you choose?

a) 2 g IV 8/8 h

b) 1 g IV 6/6h

c) I calculate the dose according to body weight and creatinine clearance

d) 2 g IV 12/12 h

e) I calculate the dose according to the body surface area

Correct answer: C

Pharmacokinetic and pharmacodynamic studies have established the following parameters to calculate the dose, schedule and duration of infusion of betalactam antibiotics: body weight, creatinine clearance and the minimum inhibitory concentration of the bacteria causing infection.[6] On the other hand, neutropenic patients may present with low (e.g., patients with multiple myeloma) or high creatinine clearance (children and young adults receiving hyperhydration for chemotherapy). The administration of betalactam antibiotics at a fixed dose may result in under or overexposure to the antibiotic.

4. A patient with a diagnosis of acute myeloid leukemia is admitted for induction chemotherapy and presents with dyspnea. The white blood cell count is 125,000/mm^3, and platelet count is 8,000/mm^3. A chest CT scan shows diffuse alveolar infiltrates and pleural effusion. What is the less likely diagnosis?

a) Invasive aspergillosis

b) Leukemic infiltration in the lungs

c) Pulmonary hemorrhage

d) Bacterial pneumonia

e) Diffuse alveolar damage

Correct answer: A

Lung infiltrates in patients with acute leukemia have different etiologies, including leukemic infiltration in the lungs, hemorrhage and infection.[7] For the differential diagnosis, two parameters should be considered: timing of the appearance of tung infiltrates (early or late during the treatment) and the pattern of lung involvement (localized or diffuse). Invasive aspergillosis presents with localized infiltrates.[8]

5. Mark the wrong sentence regarding antifungal agents

a) The azoles are the class of antifungal agents with the highest incidence of drug interactions

b) Posaconazole should not be given together with vincristine

c) The main indication of posaconazole is in primary prophylaxis in acute myeloid leukemia

d) Serum levels of voriconazole may suffer variations independent of the route of administration (oral or intravenous)

e) Echinocandins are active against *Candida*, *Aspergillus* and *Cryptococcus*

Correct answer: E

Among the antifungal classes, azoles have the highest incidences of drug interactions, by inhibiting the main metabolic pathway of the large majority of drugs (CYP3A4).[2] Vincristine is metabolized by CYP3A4, and the concomitant use of posaconazole, which is a strong CYP3A4 inhibitor, results in an unacceptable increase in the risk of neurologic toxicity of vincristine.[9] Posaconazole is the drug of choice for primary prophylaxis in acute myeloid leukemia.[3] The main determinant of

unpredictable serum levels of voriconazole is polymorphisms in the CYP2C19, the main metabolic pathway of voriconazole.[10] The echinocandins are active against *Candida* and *Aspergillus* but not *Cryptococcus*.[11]

6. An autologous hematopoietic cell transplant (HCT) recipient develops febrile neutropenia on day +1 and started on piperacillin-tazobactam. On day 4 of antibiotic the patient remains febrile, but blood cultures are negative, the patient has no complains and the physical exam is unremarkable. What is the most appropriate action?

a) Obtain blood cultures and add vancomycin

b) Obtain blood cultures and keep piperacillin-tazobactam

c) Obtain blood cultures and start lipid amphotericin B and vancomycin

d) Obtain blood cultures and change antibiotic to meropenem, vancomycin and tigecycline

e) Obtain blood cultures and change antibiotic to meropenem

Correct answer: B

Neutropenic patients with persistent fever but clinically stable should keep the antibiotic regimen unchanged unless there is a new clinical sign of infection or if blood cultures are positive.[12] Furthermore, the median time to defervescence in febrile neutropenia is five days.[13] Therefore, persistent fever in a stable neutropenic patient is not a criterion for change in the empiric antibiotic regimen. The empiric addition of vancomycin is not supported by randomized clinical trials.[14]

7. The most frequent Gram-negative bacteria causing bloodstream infections in neutropenic patients are:

a) *Escherichia coli*, *Klebsiella* and *Serratia*

b) *Pseudomonas aeruginosa*, *Klebsiella* and *Escherichia coli*

c) *Morganella*, *Proteus* and *Pseudomonas aeruginosa*

d) *Serratia*, *Acinetobacter* and *Escherichia coli*

e) *Pseudomonas aeruginosa*, *Enterobacter* and *Proteus*

Correct answer: B.[15,16]

8. In which situation below would you consider deoxycholate amphotericin B as the drug of choice?

a) Empiric therapy of candidemia

b) Treatment of invasive aspergillosis

c) Treatment of candidemia in patients who present intolerance to fluconazole

d) Empiric therapy of febrile neutropenic patients

e) None of the above

Correct answer: E

Deoxycholate amphotericin B should not be used in any of these situations in a hematologic patient because of unacceptable toxicity and because lipid formulations of amphotericin B have a more favorable safety profile.[17,18]

9. A febrile neutropenic patient is receiving cefepime. Blood cultures grow methicillin-susceptible *Staphylococcus aureus*. The absolute neutrophil count is 50/mm^3. What is your action?

a) Add vancomycin

b) Keep cefepime

c) Discontinue cefepime and start vancomycin

d) Discontinue cefepime and start oxacillin

e) Add linezolid

Correct answer: B

Cefepime is a 4th generation cephalosporin with broad spectrum that includes methicillin susceptible *Staphylococcus aureus*.[19] Therefore, there is no need to add another anti-Gram-positive antibiotic. On the other hand, the betalactam antibiotic should be continued throughout the episode of febrile neutropenia once a bloodstream infection was diagnosed.

10. An autologous HCT recipient is on day +10 post-transplant, on the 7th day of empiric antibiotic therapy for febrile neutropenia receiving cefepime and presents a new fever after 5 days without fever. In addition, he presents tachypnea, and a skin rash in the trunk. What is your action?

a) Discontinue cefepime and start meropenem

b) Add voriconazole

c) Add vancomycin

d) Start ganciclovir

e) Start corticosteroids

Correct answer: E

Engraftment syndrome is a complication of autologous HCT that occurs close to the engraftment period. Diagnostic criteria include: non-infectious fever (major criterion), skin rash, lung infiltrates or diarrhea (minor criteria).[20] Other clinical manifestations include weight gain and neurologic symptoms. Although in many cases the clinical manifestations are mild, with spontaneous resolution of symptoms, more severe cases should be treated with corticosteroids.[21]

11. Mark the wrong sentence regarding the different preparations of amphotericin B

a) The efficacy of deoxycholate amphotericin B is superior compared to the lipid formulations

b) Deoxycholate amphotericin B is the preparation associated with the highest frequency of renal toxicity

c) The frequency of acute adverse events (fever, rigors) is similar compared to lipid complex and deoxycholate amphotericin B

d) Liposomal amphotericin B is the less toxic preparation

e) Anemia may occur as an adverse event of amphotericin B

Correct answer: A

The efficacy of deoxycholate amphotericin B is not superior compared with the other preparations, but is the one with the highest rates of side effects, that include acute adverse events (fever, chest pain, rigors, etc.), renal toxicity (including hypokalemia) and bone marrow toxicity, especially anemia.[18] Amphotericin B lipid complex is associated with less renal toxicity compared with deoxycholate amphotericin B, but the frequency of acute adverse events is similar. Liposomal amphotericin B is the preparation with fewer side effects.[22]

12. An autologous HCT recipient is on day +11, on the 4th day of cefepime for febrile neutropenia. Baseline blood cultures were negative, and the absolute neutrophil count is 1,200/mm^3. The patient is afebrile. What is your action?

a) Keep cefepime for three additional days for a total duration of 7 days

b) Switch to ciprofloxacin and keep until a total duration of 10 days of antibiotics

c) Keep cefepime for two additional days after engraftment

d) Discontinue cefepime immediately

e) Switch to ciprofloxacin until discharge

Correct answer: D

When neutropenia is resolved and there was no clinical or microbiologic documentation of infection, the antibiotic regimen should be discontinued regardless of the duration of antibiotic therapy.[12]

13. Mark the wrong sentence regarding galactomannan

a) The sensitivity in the serum of neutropenic patients is high for the diagnosis of invasive aspergillosis

b) The test may be positive in invasive fusariosis

c) Serum galactomannan is useful to monitor treatment response

d) A value >0.7 in the bronchoalveolar lavage is diagnostic of aspergillosis

e) High values in the serum are associated with poorer outcome

Correct answer: D

Galactomannan is a polysaccharide released by the cell wall of *Aspergillus* and a few other molds. It is an important tool for the diagnosis and monitoring of treatment in hematologic patients with invasive aspergillosis. In neutropenic patients, the sensitivity and specificity are >90%.[23] Although considered specific for aspergillosis, the test may be positive in other mold infections, including invasive fusariosis.[24] In a patient with invasive aspergillosis, fast normalization of serum galactomannan is associated with treatment success, while persistently positive serum galactomannan tests indicate therapeutic failure.[25] The accepted cutoff for galactomannan in the bronchoalveolar lavage is 1.0.[26]

14. What option do you choose as primary therapy for invasive aspergillosis?

a) Voriconazole + anidulafungin

b) Deoxycholate amphotericin B 1 mg/kg/d

c) Deoxycholate amphotericin B 0.7 mg/kg/d + micafungin

d) Voriconazole

e) Liposomal amphotericin B 10 mg/kg/d

Correct answer: D

Voriconazole was superior to deoxycholate amphotericin B in the treatment of invasive aspergillosis, and is considered the treatment of choice.[27] More recently, two other azoles (isavuconazole and posaconazole) were compared with voriconazole in randomized trials of non-inferiority, and are considered alternatives to voriconazole in

the treatment of invasive aspergillosis.[28,29] Combination therapy with voriconazole and anidulafungin was not superior to voriconazole alone in a randomized trial.[30] Liposomal amphotericin B at a dose of 10 mg/kg/d was not superior to a dose of 3 mg/kg/d and was more toxic in a randomized trial.[31]

15. A patient with acute lymphoid leukemia relapses is in the 9th day of antibiotic for febrile neutropenia. He presents with myalgias, and the physical exam shows three erythematous nodules in the skin. What is the most likely diagnosis?

a) Infection by *Pseudomonas aeruginosa*

b) Invasive fusariosis

c) Invasive aspergillosis

d) Chronic disseminated candidiasis

e) Disseminated herpes simplex

Correct answer: B

Skin nodules in a neutropenic patient with acute leukemia are very suspicious of invasive fusariosis, with myalgia and the appearance of erythematous nodules that evolve with central necrosis.[32] The fastest way of establishing the diagnosis is to perform skin biopsy, with direct exam, culture and histopathology.

16. A neutropenic patient with acute leukemia presents with positive serum galactomannan and a pulmonary nodule. A diagnosis of invasive pulmonary aspergillosis is made and treatment is promptly initiated with an azole. A chest CT scan performed 1 week after the diagnosis shows increase in the volume of the lung nodule despite treatment. What is your action?

a) Check serum galactomannan and if the values returned to normal (<0.5), I do not change treatment

b) I add an echinocandin

c) I change to lipid amphotericin B

d) I check susceptibility test and change the treatment accordingly

e) I add lipid amphotericin B

Correct answer:

An immune reconstitution syndrome with worsening symptoms and images in chest CT scan may occur in neutropenic patients when the neutrophil count increases.[33] A study evaluating serial CT scans in hematologic patients with aspergillosis showed that an increase in the volume of lesions after the first week of treatment was frequent, and not associated with treatment failure.[34] In the case presented, checking the galactomannan curve helps to differentiate between treatment failure and immune reconstitution, with rising values being associated with treatment failure.[25,35] Patients who have severe symptoms (e.g., dyspnea, hypoxemia) with the immune reconstitution syndrome may improve with corticosteroids (prednisone 2 mg/kg 2-3 days).[36]

17. In a patient with normal white blood cell counts and normal bone marrow, which chemotherapeutic regimen results in shorter duration of neutropenia?

a) High-dose cytarabine

b) CHOP

c) COP

d) Prednisone, vincristine and asparaginase

e) ABVD

Correct answer: D

Prednisone, vincristine and L-asparaginase are not myelotoxic, while all other regimens have at least one chemotherapeutic agent with myelotoxicity (cytarabine, cyclophosphamide, doxorubicin, vinblastine and dacarbazine).

18. The microbiology laboratory informs that yeasts suggestive of *Candida* were observed in the direct exam of a positive blood culture. What is your action?

a) Start treatment immediately

b) Check how many bottles of blood culture are positive

c) Wait the identification of the yeast and then start treatment

d) Change venous access and obtain new blood cultures

e) Ask for urine culture and decide on the basis of the result

Although transient candidemia may occur, every patient with positive blood cultures for *Candida* spp. should be treated immediately [37].

19. A patient with acute myeloid leukemia presents fever, abdominal pain and diarrhea on the 16th day of induction remission. What finding in the abdominal CT scan is more compatible with a diagnosis of typhlitis?

a) Dilation of the transverse colon

b) Mild ascites

c) Dilation of the cecum

d) Thickening of the small bowel wall

e) Fluid around the gallbladder

Correct answer: D

Thickening of the small bowel wall is the more specific radiologic sign of typhlitis,[38] being one of the diagnostic criteria, together with neutropenia and fever.[39]

20. A patient developed candidemia in a previous cycle of chemotherapy, and was successfully treated. In the next cycle of chemotherapy, you:

a) Give fluconazole to prevent recurrence of candidemia

b) Obtain weekly blood cultures to diagnose recurrence

c) Does not take any special action because the risk of recurrence is low

d) Give fluconazole only if candidemia was caused by *Candida glabrata*

e) Give voriconazole only if candidemia was caused by *Candida glabrata*

Correct answer: C

Different from invasive aspergillosis, where secondary prophylaxis is indicated to prevent relapse,[2] there are no data suggesting that a patient who developed candidemia in a previous cycle of chemotherapy and received adequate treatment is at high risk of recurrence.

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Supplementary file 2: Infection in hematopoietic cell transplantation (HCT)

1. A patient is on day +97 of an HLA matched related-donor allogeneic HCT, receiving corticosteroids and cyclosporine for the treatment of chronic graft versus host disease (GVHD). The day before he presented with fever and a chest X-ray showed alveolar infiltrates in the middle 1/3 of the right lung. What is the most likely diagnosis?

a) *Pneumocystis jirovecii* pneumonia

b) Invasive aspergillosis

c) *Streptococcus pneumoniae* pneumonia

d) *Staphylococcus aureus* pneumonia

e) CMV pneumonia

Correct answer: C

Pneumonia is a frequent complication of allogeneic HCT. The most frequent agents are bacteria. Patients with chronic GVHD usually have hypogammaglobulinemia, increasing the risk of infection by encapsulated bacteria such as *Streptococcus pneumoniae*.[1,2]

2. An allogeneic HCT recipient is receiving antifungal prophylaxis with fluconazole in the pre-engraftment period. The microbiology laboratory informs that blood cultures are positive for *Candida* species. What is the most likely species?

a) *Candida tropicalis*

b) *Candida guilliermondii*

c) *Candida albicans*

d) *Candida famata*

e) *Candida krusei*

Correct answer: E

Patients under prophylactic fluconazole are at higher risk to develop candidemia due to less-fluconazole-susceptible species such as *Candida glabrata* and *Candida krusei*.[3]

3. Which of option is not a risk factor for invasive aspergillosis?

a) Gastrointestinal mucositis

b) Iron overload

c) Graft versus host disease prophylaxis with anti-thymocyte globulin

d) Influenza pneumonia

e) Cytomegalovirus reactivation

Correct answer: A

Important risk factors for invasive aspergillosis after allogeneic HCT include CMV reactivation, respiratory viral infection, such as influenza, GVHD and its treatment, and prolonged neutropenia, among others.[4,5] Gastrointestinal mucositis is a risk factor for candidemia but not aspergillosis.[6]

4. Mark the wrong option regarding CMV post HCT

a) The risk is higher with unrelated cord blood transplant

b) Primary prophylaxis until D+100 may result in the occurrence of late onset CMV

c) CMV Pneumonia is more severe in allogeneic compared with autologous HCT

d) The use of ganciclovir increases the risk for bacterial and fungal infection

e) High dose acyclovir may prevent CMV reactivation

Correct answer: C

Risk factors for CMV reactivation post HCT include: donor and recipient serostatus, HLA mismatch, cord blood transplant, receipt of high doses of corticosteroids, T cell depletion and GVHD. Primary prophylaxis until D+100 may result in CMV reactivation when prophylaxis is discontinued. Neutropenia is an important side effect of ganciclovir, and its occurrence. High-dose acyclovir may prevent CMV reactivation. Finally, once CMV pneumonia occurs, it is as severe in autologous as in allogeneic HCT.[7-9]

5. A patient presents respiratory symptoms on D+13 of myeloablative allogeneic HCT. Chest CT scan shows diffuse infiltrates in both lungs. Which etiology is unlikely?

a) Influenza pneumonia

b) Pneumonitis caused by the conditioning regimen

c) Engraftment syndrome

d) Invasive aspergillosis

e) Fluid overload

Correct answer: D

The differential diagnosis of diffuse lung infiltrates in allogeneic HCT recipients includes infectious causes (viral, pneumocystis, atypical pneumonia), and non-infectious (fluid overload, engraftment syndrome, drug toxicity and others. By contrast, invasive aspergillosis is a focal lung disease.[10,11]

6. The most frequent viral disease after engraftment in autologous HCT is:

a) Herpes simplex labialis

b) Herpes zoster

c) CMV reactivation

d) EBV reactivation

e) BK virus reactivation

Correct answer: B

Herpes zoster is the most frequent viral infection after engraftment of autologous HCT, occurring in approximately 30% of patients. The highest incidence is in the first year post transplant.[12]

7. Choose the correct sentence regarding invasive aspergillosis in allogeneic HCT

a) Serum galactomannan has poor performance in neutropenic patients

b) Isavuconazole and voriconazole are therapeutic options as first line

c) Nodular skin lesions are frequent

d) The most frequent image in patients with GVHD is a nodule with halo sign

e) The majority of cases occur in the pre-engraftment period (until Day +30)

Correct answer: B

Aspergillosis is the most frequent invasive fungal disease in allogeneic HCT recipients, and occurs both in the pre and post-engraftment periods. Serum galactomannan has a good performance in neutropenic patients. Different from fusariosis, nodular skin lesions are very uncommon. In patients with GVHD, the typical images are of bronchial dissemination, with centrilobular micro (<1 cm) nodules and tree in bud infiltrates. Isavuconazole and voriconazole are options for primary therapy.[13-15]

8. Which is the wrong sentence regarding antibiotics in febrile neutropenia?

a) Piperacillin-tazobactam has anti-anaerobic action

b) Meropenem has no activity against *Stenotrophomonas maltophilia*

c) Cefepime has activity against methicillin-sensitive *Staphylococcus aureus*

d) Meropenem has activity against methicillin-resistant *Staphylococcus aureus*

e) Meropenem has activity against ESBL-producing enterobacteria

Correct answer: D

Meropenem is a broad spectrum antibiotic, but has no activity against methicillin-resistant *Staphylococcus aureus*.[16]

9. Which of the scenarios below is not at risk for EBV reactivation?

a) Allogeneic HCT with HLA mismatch

b) Use of antithymocyte globulin

c) Cord blood transplant

d) Pre-transplant alemtuzumab

e) Pre-transplant rituximab

Correct answer: E

Post-transplant EBV reactivation occurs more frequently with T-cell depletion, such as ATG, cord blood, altmtuzumab and HLA mismatch. By contrast, rituximab is used in the treatment of EBV-associated lymphoproliferative disease.[17]

10. An autologous HCT recipient is on day +10 post-transplant and in the 7th day of empiric cefepime for febrile neutropenia. He is afebrile since the third day of antibiotic. Today he presents with fever (38,6°C), tachypnea and a non-pruriginous diffuse skin rash in the trunk. What is your action?

a) Discontinue cefepime and start meropenem

b) Add voriconazole

c) Add vancomycin

d) Start systemic corticosteroids

e) Start ganciclovir

Correct answer: D

Engraftment syndrome is a complication of autologous hematopoietic cell transplantation that occurs close to the engraftment period. Diagnostic criteria include: non-infectious fever (major criterion), skin rash, lung infiltrates or diarrhea (minor criteria). Other clinical manifestations include weight gain and neurologic symptoms. Although in most cases the clinical manifestations are mild, with spontaneous resolution of symptoms, more severe cases should be treated with corticosteroids.[18,19]

11.Regarding CMV monitoring post allogeneic HCT, mark the correct statement:

a) CMV reactivation occurs between day 21 and 100 post-transplant

b) The cutoff for quantitative PCR to trigger the initiation of preemptive therapy should be defined in each institution, according to the population at risk and the laboratory platform used

c) 10,000 copies/mL is the accepted cutoff for preemptive therapy

d) CMV monitoring should be performed until day +100 in all allogeneic HCT recipients

e) CMV monitoring should be done twice a week between day +30 and day +60 post allogeneic HCT

Correct answer: B

CMV monitoring post allogeneic HCT should be performed at least once a week until day +100, and beyond there is active GVHD. There is no established cutoff for triggering preemptive therapy, and the definition of the cutoff must be individualized, considering the platform used to perform PCR. CMV reactivation may occur before engraftment.[20]

12. An autologous HCT recipient develops fever on day +2, cefepime is started and the patient becomes afebrile. On day +5 the patient is still afebrile, has no clinical signs of infection, but the microbiology laboratory informs that blood cultures are positive for extended spectrum betalactamase (ESBL)-producing *Escherichia coli*,

with a minimum inhibitory concentration of 1 microgram per ml for cefepime, what is your action?

a) Keep cefepime

b) Switch to meropenem

c) Switch to piperacillin-tazobactam

d) Add tigeciclin

e) Add daptomycin

Correct answer: A

In stable patients, bacteremia caused by ESBL-producing enterobacteria can be treated with cefepime or piperacillin-tazobactam. According to the EUCAST (European Committee on Antimicrobial Susceptibility Testing), treatment with cefepime is possible provided that MIC is ≤1 μg/mL.[21]

13. On day +9 after allogeneic HCT, the microbiology laboratory informs that a mold is growing from blood cultures. What is your interpretation?

a) Must be contamination, I obtain new blood cultures

b) Must be aspergillosis, I start treatment

c) Must be fusariosis, I start treatment

d) I wait for the identification of the mold

e) Must be mucormycosis, I start treatment

Correct answer: C

Filamentous fungi growing in blood cultures of hematologic patients should be interpreted as diagnostic of fusariosis until proven otherwise, and treatment should be started immediately.[22]

14. Regarding BK poliomavirus in allogeneic HCT, mark the correct option:

a) Causes hemorrhagic cystitis

b) Stenosis of the ureter is a frequent manifestation

c) Computed tomography of the bladder is not useful to diagnose hemorrhagic cystitis

d) The diagnosis of BK virus-associated hemorrhagic cystitis is based on clinical signs, hematuria, and detection of the virus in the urine by quantitative PCR

e) BK virus monitoring with quantitative PCR in the urine and blood is recommended in allogeneic HCT recipients

Correct answer: D

Causes of hemorrhagic cystitis after allogeneic HCT include toxicity by the conditioning regimen (cyclophosphamide, radiotherapy, busulfan), BK polyomavirus, cytomegalovirus and JC polyomavirus. The most frequent clinical manifestations are dysuria, hematuria and suprapubic pain. Imaging such as ultrasonography and computed tomography may help in the differential diagnosis. Routine screening is not recommended because high viral load does not correlate with the development of hemorrhagic cystitis.[23]

15. In which situation below do you consider a lipid formulation of amphotericin B the drug of choice?

a) Empiric therapy of candidemia

b) Primary therapy of invasive aspergillosis

c) Primary therapy of mucormycosis

d) Primary therapy of candidemia caused by *Candida glabrata*

e) None of the above

Correct answer: C

The agents of choice for primary therapy of mucormycosis are a lipid formulation of amphotericin B or isavuconazole. Primary therapy for candidemia and aspergillosis are echinocandins and voriconazole or isavuconazole, respectively.[24]

16. Regarding Epstein-Barr virus (EBV) reactivation after HCT, mark the correct:

a) Reduction in the immunosuppression is recommended in case of EBV DNAemia

b) Monitoring for EBV reactivation is recommended to all allogeneic HCT recipients

c) Post-transplant lymphoproliferative disease (PTLD) is the most frequent clinical manifestation of EBV reactivation

d) If monitoring with PCR is not available, the patient should receive monthly immunoglobulin replacement

e) The presence of EBV DNAemia indicates a high risk for PTLD and the need of treatment with rituximab

Correct answer: A

EBV reactivation after allogeneic HCT is associated with severe T-cell immunodeficiency. High risk for reactivation includes HLA mismatch, cord blood, T-cell depletion and GVHD. Monitoring is recommended to high-risk patients. There are no recommendations for immunoglobulin replacement in the context of EBV reactivation. Likewise, there is no cutoff for EBV DNAemia above which the risk of PTLD increases. If EBV reactivation is documented, reduction in the immunosuppression is the correct action.[25]

17. Vancomycin should be given to febrile neutropenic HCT recipients in case of:

a) Erythema in the catheter exit site

b) Documentation of infection by methicillin-resistant *Staphylococcus aureus*

c) Grade 3-4 oral mucositis

d) Persistent fever after 3 days of betalactam antibiotic

e) All of the above

Correct answer: B

Neutropenic patients with persistent fever but clinically stable should not have the antibiotic regimen changed unless an infection is documented by a pathogen that is resistant to the regimen.[26] The empiric addition of vancomycin to persistently febrile patients did not show any benefit in a randomized trial.[27] Vancomycin should be added if there is documentation of infection by methicillin-resistant *Staphylococcus aureus*.

18. Mark the correct answer regarding the treatment of invasive fungal diseases

a) Voriconazole is the agent of choice for the treatment of candidemia caused by fluconazole-resistant species

b) Amphotericin B is superior to voriconazole in the primary therapy of invasive fusariosis

c) Invasive aspergillosis should be treated for at least 6 weeks

d) In the treatment of invasive aspergillosis, treatment response is superior with higher doses of liposomal amphotericin B (10 mg/kg/d)

e) Mucormycosis can be treated with isavuconazole

Correct answer: E

Fluconazole and voriconazole present cross resistance. The drug of choice for the treatment of fluconazole-resistant *Candida* species is echinocandin. For aspergillosis, isavuconazole or voriconazole are options, the duration of treatment should be individualized.[24] Lipid amphotericin B is not superior to voriconazole in the treatment of fusariosis.[28] Isavuconazole is an option in the treatment of mucormycosis.[29]

19. A HCT recipient is under prophylactic acyclovir and fluconazole, and empiric antibiotic therapy with cefepime for febrile neutropenia. A diagnosis of typhlitis was made. How do you adjust the antimicrobial regimen?

a) Broaden spectrum to cover anaerobic bacteria

b) Broaden spectrum to cover multi-drug-resistant Gram-negative bacteria

c) Increase the dose of acyclovir

d) Broaden the spectrum of antifungal therapy

e) All the above

Correct answer: A

Patients with a diagnosis of typhlitis should receive anti-Gram-negative and anti-anaerobic antibiotics.[30]

20. Regarding respiratory viral infections in allogeneic HCT recipients, mark the correct option:

a) A search for respiratory viruses in the serum should be undertaken in case of respiratory symptoms

b) Upon suspicion of influenza, we should wait for the confirmation of the diagnosis before starting oseltamivir

c) Inhaled, oral or intravenous ribavirin is the treatment of choice for parainfluenza and respiratory syncytial virus (RSV) infection

d) Infection by parainfluenza virus rarely causes pneumonia

e) If a diagnosis of RSV is made before admission for HCT, the procedure should be postponed

Correct answer: E

Search for respiratory viruses should be undertaken in symptomatic patients, using nasal swab or nasal wash, tracheal aspirate or bronchoalveolar lavage.[31] Oseltamivir should be started empirically if there is suspicion of influenza. The treatment of choice for RSV is oral ribavirin.[32] Infection by parainfluenza virus evolve to pneumonia in 20-30% of patients.

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APÊNDICE 2

Artigo 2: “Early versus Late Fluconazole Prophylaxis in Autologous Hematopoietic Cell Transplantation”

Transplantation and Cellular Therapy 27 (2021) 681.e1–681.e5

Transplantation and Cellular Therapy

journal homepage: www.tctjournal.org

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Full Length Article
Infectious Disease

Early versus Late Fluconazole Prophylaxis in Autologous Hematopoietic Cell Transplantation

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Article history:
Received 17 March 2021
Received in revised from 16 April 2021
Accepted 25 April 2021

Key Words:
Fluconazole
Prophylaxis
Mucositis
Autologous transplantation
Candidemia
Hematopoietic cell transplantation

ABSTRACT

Candidemia is a major complication in hematopoietic cell transplantation (HCT), and antifungal prophylaxis with fluconazole decreases the incidence of this complication. We compared 2 strategies for fluconazole prophylaxis in patients with hematologic malignancy undergoing autologous HCT between 1997 and 2017. From 1997 to 2003, fluconazole prophylaxis (400 mg/d) was given to all HCTs, started with the conditioning regimen (early prophylaxis), and given until neutrophil engraftment or the need of non-prophylactic antifungal therapy. From 2004 on, fluconazole (400mg daily) was started only if (and when) the patient developed oral mucositis (late prophylaxis). Among 571 HCT, 270 received early prophylaxis, 112 received late prophylaxis, and 189 did not receive fluconazole because they did not develop oral mucositis. The incidence of candidemia was 1.8% in the early prophylaxis group, 0% in the late prophylaxis group, and 1.1% in the no prophylaxis group ($P = .31$). Among patients receiving fluconazole, the median duration of prophylaxis was 17 days (range, 6-36 days) in the early prophylaxis group and 6 days (range, 2-16 days) in the late prophylaxis group ($P < .001$). The initiation of fluconazole prophylaxis guided by the occurrence of oral mucositis (late prophylaxis) was as good as early fluconazole prophylaxis.

INTRODUCTION

Invasive fungal disease (IFD) is a serious complication in hematopoietic cell transplantation (HCT) recipients [1]. Historically, *Candida* species have been the most frequent causative agents of IFD, with a high mortality rate [2,3]. Randomized trials evaluating the efficacy of fluconazole as prophylaxis showed a significant decrease in the incidence of candidemia in fluconazole recipients, especially in allogeneic HCT [4-6]. Accordingly, fluconazole prophylaxis became standard of care in the preengraftment period of allogeneic HCT, with a high strength of recommendation. Regarding autologous HCT, the guidelines suggest the use of fluconazole in certain circumstances, acknowledging the fact that the risk for invasive candidiasis is lower [7,8]. Yet, fluconazole prophylaxis is routinely used in many centers worldwide [9-16].

The main source of candidemia is the gut [17]. In HCT recipients, disruption of the intestinal mucosal barrier caused by the conditioning regimen increases the risk of translocation of *Candida* species from the intestinal lumen to the bloodstream, causing candidemia [18].

From the beginning of our HCT program, fluconazole prophylaxis has been given as prophylaxis, starting with the conditioning regimen and discontinuing after engraftment or the initiation of another antifungal agent used as empiric therapy or on documentation of a fungal infection. In 2004, we decided to change our routine and started to give fluconazole only if and when a patient developed oral mucositis. Here we report our experience with this practice of late fluconazole prophylaxis.

METHODS

This retrospective study was conducted at Hospital Universitário Clementino Fraga Filho, Federal University of Rio de Janeiro, Brazil, a university-affiliated tertiary care hospital. The Hematology Unit has 8 single-bed rooms with high-efficiency particulate air (HEPA) filtration and positive pressure and 5 double-bed rooms without HEPA filtration. The study was approved by the hospital's Ethical Committee (Study 077-16).

All data regarding the episode of febrile neutropenia during the early preengraftment period were collected prospectively, using a case report form with the help of a dictionary of terms. For this study, we reviewed the episodes of febrile neutropenia of all autologous HCTs performed between 1997 and 2017 for the treatment of hematologic malignancies. From 1997 to 2003, antifungal prophylaxis consisted of fluconazole (400 mg/day) started with the conditioning regimen (early prophylaxis), and given until the patient experienced neutrophil engraftment or required nonprophylactic antifungal therapy (empiric or for the treatment of a documented IFD). Starting in 2004, routine prophylaxis was discouraged. Instead, fluconazole (400 mg/day) was started only if (and when) the patient developed grade ≥2 oral mucositis (late prophylaxis). Oral mucositis was assessed daily and recorded prospectively, using the

Financial disclosure: See Acknowledgments on page 681.e4.

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https://doi.org/10.1016/j.jtct.2021.04.019
2666-6367/

National Cancer Institute Common Toxicity Criteria [19]. Patients receiving antifungal prophylaxis other than fluconazole were excluded.

The following variables were analyzed: baseline characteristics, conditioning regimen, antibacterial prophylaxis, duration of fluconazole prophylaxis, empiric antibiotic regimen, classification of the febrile episode, IFD, duration of neutropenia, and death. We hypothesized that late prophylaxis was as effective as early prophylaxis. To test our hypothesis, we compared underlying diseases, conditioning regimen, the presence of oral mucositis, documentation of candidemia, duration of neutropenia, duration of fluconazole prophylaxis, and outcomes in 3 groups: patients who received early prophylaxis, those who received late prophylaxis, and those who received no prophylaxis.

Neutropenia was defined as an absolute neutrophil count of $<500/mm^3$, and fever was defined as an axillary temperature of >38 °C. The episodes of febrile neutropenia were classified as fever of unknown origin, bacteremia, microbiologically documented without bacteremia, or clinically documented, as described previously [20]. Candidemia was defined by a blood culture with *Candida* species in a patient with fever and/or clinical signs of infection [21].

Categorical variables were compared using the chi-square or Fisher exact test as appropriate, and continuous variables were compared using the Kruskal-Wallis test. All analyses were performed using SPSS 21.0 for Windows (IBM, Armonk, NY).

RESULTS

During the study period, 583 autologous HCTs were performed in patients with hematologic disease. Twelve HCT recipients received other prophylactic regimens (itraconazole in 5, voriconazole in 4, posaconazole in 3) and were excluded. The remaining 571 HCTs were performed in 559 patients (12 patients received 2 transplants). The median age of the 559 patients was 49 years (range, 7 to 72 years), and 314 (56.2%) were male. The characteristics of the 571 autologous HCTs are shown in Table 1. The most frequent underlying disease was multiple myeloma (54.1%), followed by Hodgkin's lymphoma (24.0%) and non-Hodgkin's lymphoma (18.2%). Prophylactic quinolone was used in 255 patients (44.6%). Fluconazole prophylaxis was used in 382 HCTs (66.9%); early prophylaxis, in 270 HCTs; and late prophylaxis, in 112 HCTs.

The most frequent antibiotic regimen given at first fever was cefepime monotherapy (474 episodes; 83%).

Table 1
Baseline Characteristics of 571 Autologous HCTs

Characteristic	No. (%)
Underlying disease	
Multiple myeloma	309 (54.1)
Hodgkin lymphoma	137 (24.0)
Non-Hodgkin lymphoma	104 (18.2)
Acute myelogenous leukemia	15 (2.6)
Other*	6 (1.1)
Conditioning regimens	
Melphalan-based regimen†	313 (54.8)
CBV	188 (32.9)
BEAM	46 (8.1)
Other‡	24 (4.2)
Quinolone prophylaxis	255 (44.6)
Antifungal prophylaxis	
Early prophylaxis	270 (47.3)
Late prophylaxis	112 (19.6)
No prophylaxis	189 (33.1)

CBV indicates cyclophosphamide, carmustine, etoposide; BEAM, carmustine, cytarabine, etoposide, melphalan.

* Other underlying diseases: amyloidosis (n = 4), acute lymphoblastic leukemia (n = 2).

† Melphalan-based regimen: 200 mg/m^2 (n = 271), 140 mg/m^2 (n = 27), 100 mg/m^2 (n = 15).

‡ Other conditioning regimens: busulfan + cyclophosphamide (n = 14); busulfan + cyclophosphamide + etoposide (n = 7); carmustine + etoposide + cytarabine + cyclophosphamide (n = 3).

Table 2
Episodes of IFD during Neutropenia in 571 Autologous HCTs

IFD	No. (%)
Candidemia	6 (1.1)
Candida tropicalis	2
Candida parapsilosis	2
Candida albicans	1
C. krusei	1
Fungemia due to *Exophiala jeanselmei**	4 (0.7)
Aspergillosis	3 (0.5)
Fusariosis	3 (0.5)
Mucormycosis	1 (0.2)
Candidemia [*C. tropicalis*] + fungemia due to *E. jeanselmei**	1 (0.2)
Fungemia due to *Rhodotorula rubra*	1 (0.2)

* Cases of fungemia due to *E. jeanselmei* occurred in the context of an outbreak [34].

Nonprophylactic antifungal therapy was given in 51 HCTs (8.9%): as empiric therapy in 25, to treat oral candidiasis in 14, and to treat IFD in 12. Clinical or microbiologic documentation of infection was recorded in 48.9% of the HCTs. The median duration of neutropenia was 8 days (range, 2 to 31 days), and 31 deaths occurred (5.4%). Overall, IFD was diagnosed in 19 HCTs (3.3%), including 7 episodes of candidemia (1 of which was a mixed infection) (Table 2).

Table 3 presents the characteristics and outcomes of 571 autologous HCTs according to the antifungal prophylactic regimen: early (n = 270), late (n = 112), or no (n = 189) prophylaxis. As expected, the frequency of oral mucositis was significantly lower in the no prophylaxis group (39.2%, versus 66.5% in the early prophylaxis group and 79.5% in the late prophylaxis group; $P < .001$). The median duration of fluconazole prophylaxis was 17 days (range, 6 to 36 days) in the early prophylaxis group and 6 days (range, 2 to 16 days) in the late prophylaxis group ($P < .001$). Of note, candidemia occurred in 5 HCTs (1.8%) in the early prophylaxis group, in no HCTs in the late prophylaxis group, and in 2 HCTs (1.1%) in the no prophylaxis group (P= .31). There were no differences in death rate across the 3 groups.

DISCUSSION

In this study, we found that the incidence of candidemia was not different between the early and late fluconazole prophylaxis groups, the median duration of fluconazole use was significantly reduced in the late prophylaxis, and IFD was uncommon after autologous HCT. These data indicate that the initiation of fluconazole prophylaxis in autologous HCT may be driven by the presence of oral mucositis.

Strategies to prevent the occurrence of IFD among HCT recipients have been developed with the aim of reducing the incidence and mortality of these diseases [5,6,20]. In allogeneic HCT, 2 important randomized studies comparing fluconazole with placebo showed decreases in both superficial and systemic fungal diseases with triazole, with improved survival [4,5,22]. Therefore, in centers with a low incidence of IFD caused by molds, the general recommendation is to use prophylaxis with fluconazole 400 mg/day in allogeneic HCT recipients, with a high strength of recommendation (A-I) [7,8]. In autologous HCT this recommendation is weaker (B-III), however, reflecting the much lower risk of IFD in these patients [7,8]. Nevertheless, fluconazole prophylaxis is the standard of care in autologous HCT recipients worldwide [9-16].

A remarkable finding of our study is that starting fluconazole only if (and when) a patient developed oral mucositis (late prophylaxis) worked as well as giving fluconazole to all

Table 3
Comparison of the Characteristics and Outcomes of 571 Autologous HCT Recipients According to Antifungal Prophylaxis Regimen

Characteristic	Early Prophylaxis (N = 270)	Late Prophylaxis (N = 112)	No Prophylaxis (N = 189)	*P* Value
Age, yr, median, range	49 (12-69)	53 (13-72)	49 (13-66)	.07
Sex, male/female, n	148/122	61/51	113/76	.51
Underlying disease				
Multiple myeloma	133 (49.3)	65 (58.0)	111 (58.7)	.09
Hodgkin lymphoma	68 (25.2)	27 (24.1)	42 (22.2)	.76
Non-Hodgkin lymphoma	59 (21.9)	18 (16.1)	27 (14.3)	.09
Conditioning regimen, n (%)				
Melphalan-based regimen	133 (49.2)	66 (59.0)	113 (59.8)	.05
CBV	95 (35.2)	29 (25.9)	64 (33.9)	.20
BEAM	29 (10.7)	12 (10.7)	5 (2.6)	<.001
Oral mucositis, n (%)	177 (65.6)	89 (79.5)	74 (39.2)	<.001
Duration of fluconazole prophylaxis, d, median (range)	17 (6-36)	6 (2-16)	NA	<.001*
Duration of neutropenia, d, median (range)	8 (2-31)	8 (2-28)	8 (3-24)	.46
Empiric antibiotic therapy, n (%)				
Monotherapy	204 (75.6)	94 (83.9)	171 (90.5)	<.001
Cefepime	194 (95.1)	80 (85.1)	164 (95.9)	
Carbapenem	8 (3.9)	14 (14.9)	7 (4.1)	
Other†	2 (1.0)	0	0	
Combination	66 (24.4)	18 (16.1)	18 (9.5)	
Cefepime-based	50 (75.8)	16 (88.9)	11 (61.1)	
Ceftazidime-based	10 (15.2)	0	4 (22.2)	
Carbapenem-based	2 (3.0)	0	2 (11.1)	
Other‡	4 (6.1)	2 (11.1)	1 (5.6)	
Nonprophylactic antifungal therapy, n (%)§	26 (9.6)	5 (4.5)	20 (10.6)	.17
Empiric	20 (7.4)	2 (1.8)	3 (1.6)	
Treatment of superficial fungal disease‖	0	0	14 (7.4)	
Treatment of invasive fungal disease	6 (2.2)	3 (2.7)	3 (1.6)	
Classification of the febrile episode, n (%)				.26
Fever of unknown origin	125 (46.3)	62 (55.4)	105 (55.6)	
Bacteremia	97 (35.9)	34 (30.4)	65 (34.4)	
Clinically documented	38 (14.1)	12 (10.7)	15 (7.9)	
Microbiologically documented	10 (3.7)	4 (3.6)	4 (2.1)	
Candidemia, n (%)	5 (1.8)	0	2 (1.1)	.31
Death, n (%)	12 (4.4)	10 (8.9)	9 (4.8)	.18

NA indicates not applicable.
* *P* value for the comparison between early and late prophylaxis.
† Cefpirome (n = 6), piperacillin+ tazobactam (n = 5), and ciprofloxacin (n = 2).
‡ Cefpirome + amikacin (n = 5), ciprofloxacin + amikacin (n = 1), ciprofloxacin + amikacin + vancomycin (n = 1).
§ Empiric or for the treatment of a documented superficial or IFD.
‖ Oral candidiasis.

patients starting with the conditioning regimen. Indeed, none of the patients in the late prophylaxis group developed candidemia, showing that this approach is appropriate to prevent candidemia in autologous HCT recipients.

Mucositis is one of the most common and debilitating complications of cytotoxic chemotherapy in patients undergoing HCT [23,24]. Mucositis may affect the entire gastrointestinal tract and involves 5 phases: initiation, up-regulation and message generation, amplification and signaling, ulceration, and healing [25]. The incidence of mucositis varies among different chemotherapeutic regimens, and develops in almost 90% of patients undergoing HCT [26]. Determinants of mucositis can be divided into treatment-induced (type and dose of the regimen) and patient-related factors, such as genetic variations, age, and performance status [27,28]. In autologous HCT, mucositis was reported in 75% of patients with non-Hodgkin lymphoma submitted to the BEAM protocol (carmustine, etoposide, cytarabine, melphalan), and in 20% to 35% patients with multiple myeloma receiving melphalan based-regimens [29,30]. In our study, the frequency of oral mucositis was similar among patents with lymphoma and multiple myeloma (data not shown). Therefore, the higher proportion of patients with multiple myeloma in the period of late prophylaxis might not have impacted the frequency of mucositis in the 2 periods. Disruption of the mucosal surface of the gut is a major risk factor for infection, including candidemia, in neutropenic patients [27]. Indeed, although the source of candidemia has been a matter of debate, there are many arguments favoring the gut as origin of this infection in the majority of cases [17]. In our study, grade ≥2 oral mucositis was present in 46% of patients and was used as driver to start fluconazole prophylaxis, with no differences in the incidence of candidemia compared with standard prophylaxis.

Although fluconazole prophylaxis is effective in preventing candidemia, its use is associated with a shift from highly fluconazole-susceptible to less fluconazole-susceptible *Candida* isolates. A study of 595 patients undergoing HCT showed that despite the reduction in the frequency of candidemia, patients

receiving prophylactic fluconazole were more likely to be colonized by azole-resistant *Candida* species [31]. In other study, the use of fluconazole resulted in an increased incidence of candidemia due to *Candida krusei* and *Candida glabrata* [32]. The implementation of antifungal stewardship programs is advocated to mitigate the emergence of resistance among *Candida* bloodstream isolates [33]. Our study showed that a mucositis-guided fluconazole prophylaxis strategy was able to reduce the number of patients receiving fluconazole and shorten the duration of fluconazole use from 17 to 6 days, without increasing the rate of candidemia.

In the present study, an IFD was diagnosed in 19 HCTs, for an incidence of 3.3%. Four of these 19 cases were fungemia caused by *Exophiala jeanselmei*, which occurred in the context of an outbreak in the hospital in 1997 [34]. If we excluded these cases, the incidence would be 2.6%, which is similar to that reported in other series [35–38].

Our study suffers from the limitations of a retrospective study, with comparison between noncontemporary groups of patients. In addition, we analyzed only cases of oral mucositis, based on a subjective assessment on clinical examination of the oral cavity. Therefore, the number of patients with mucositis could have been higher had we included patients with diarrhea or abdominal discomfort, 2 possible signs of mucositis in this population.

Despite these limitations, our study shows that the initiation of fluconazole prophylaxis only when (and if) oral mucositis developed was as effective as standard prophylaxis in preventing the occurrence of candidemia in autologous HCT recipients, with a significant reduction in the duration of fluconazole use.

ACKNOWLEDGMENTS

Financial disclosure: The authors have no financial conflicts of interest

Conflict of interest statement: M.N. reports receipt of personal fees from Pfizer, MSD, Astellas, Biotoscana, Basilea, Abbvie, Janssen, Amgen, Teva, and Abbott outside the submitted work. The other authors have no conflicts of interest to disclose.

Authorship statement: M.G. collected and analyzed data and drafted the manuscript. M.N. contributed to conceptualization, collected and analyzed data, and drafted the manuscript. G.B. performed all microbiology tests for the diagnosis of IFD and reviewed and approved the manuscript. J.V. and C.A. collected data and reviewed and approved the manuscript. S.A.N. contributed to conceptualization, collected data, and reviewed and approved the manuscript.

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APÊNDICE 3

Artigo 3: “Should patients with acute myeloid leukemia treated with venetoclax-based regimens receive antifungal prophylaxis?”

Leukemia Research 131 (2023) 107341

Contents lists available at ScienceDirect

Leukemia Research

journal homepage: www.elsevier.com/locate/leukres

Should patients with acute myeloid leukemia treated with venetoclax-based regimens receive antifungal prophylaxis?

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ARTICLE INFO

Keywords:
Myeloid
Acute leukemia
Venetoclax
Antifungal
Prophylaxis

ABSTRACT

Invasive fungal disease (IFD) is a major complication in patients with acute myeloid leukemia (AML) receiving intensive induction chemotherapy, and the use of anti-mold prophylaxis is considered standard of care. On the other hand, the use of anti-mold prophylaxis in AML patients receiving less-intensive venetoclax-based regimens is not well established, basically because the incidence of IFD may not be high enough to justify primary antifungal prophylaxis. Furthermore, dose adjustments in venetoclax are needed because of drug interactions with azoles. Finally, the use of azoles is associated with toxicity, including liver, gastrointestinal and cardiac (QT prolongation) toxicity. In a setting of low incidence of invasive fungal disease, the number needed to harm would be higher than the number needed to treat. In this paper we review the risk factors for IFD in AML patients receiving intensive chemotherapeutic regimens, the incidence and risk factors for IFD in patients receiving hypomethylating agents alone, and in patients receiving less-intensive venetoclax-based regimens. We also discuss potential problems with the concomitant use of azoles, and present our perspective on how to manage AML patients receiving venetoclax-based regimens without primary antifungal prophylaxis.

1. Introduction

Invasive fungal disease (IFD) is a major complication in patients with acute myeloid leukemia (AML) undergoing intensive chemotherapy, with a negative impact on the outcome [1,2]. Until the 1990 s, invasive candidiasis was the leading IFD in high-risk hematologic patients [3]. However, after the introduction of fluconazole prophylaxis, a shift in the IFD's was observed, with a decrease in invasive candidiasis and an increase in infection caused by molds, especially invasive aspergillosis [4,5]. With the introduction of mold active azoles into clinical practice, studies evaluating strategies to prevent both candidiasis and aspergillosis were developed. A randomized trial comparing posaconazole with itraconazole or fluconazole in patients with AML or myelodysplasia (MDS) undergoing induction remission showed a significant reduction in IFD overall and invasive aspergillosis [6]. Since then, posaconazole has become standard of care as antifungal prophylaxis of patients with AML or MDS undergoing intensive induction remission chemotherapy [7–9]. Indeed, the incidence of IFD during induction remission of AML may vary widely depending on the prophylactic regimen, from 2.7 % in patients under mold-active prophylaxis [10] to as high as 26 % in patients not receiving anti-mold prophylaxis [11].

In recent years, novel therapies have been incorporated in the treatment of AML, with promising results, especially for older unfit patients. Unlike conventional chemotherapy, these agents act in specific targets in the leukemic cell, without affecting normal tissues such as the mucosae. In addition, the high and fast response rates obtained with these agents may reduce the duration of neutropenia in the induction phase. Since prolonged neutropenia and gastrointestinal mucositis are important risk factors for infection, the shorter duration of neutropenia and the absence of gastrointestinal mucositis may reduce the risk of both bacterial and fungal infections. One of these new agents is venetoclax. A randomized trial enrolled treatment naïve elderly and / or unfit AML patients to receive azacitidine plus venetoclax or placebo (Viale-A). The median overall survival (primary endpoint) was 14.7 months in the azacytidine plus venetoclax arm versus 9.6 months in the azacytidine plus placebo arm. Furthermore, the rates of complete remission were significantly higher in the venetoclax arm, with a shorter time to response (1.3 versus 2.8 months) [12]. Therefore, a reflection of whether primary antifungal prophylaxis is needed in elderly and/or unfit AML patients receiving treatment with venetoclax plus azacytidine

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https://doi.org/10.1016/j.leukres.2023.107341
Received 28 April 2023; Received in revised form 10 June 2023; Accepted 12 June 2023
Available online 14 June 2023

Table 1
Studies reporting invasive fungal disease in patients receiving hypomethylating agents.

Author, year	Number of patients	Disease	Antifungal prophylaxis	Proven or probable IFD	Comments
Merkel, 2013 [37]	184 (157 MDS); 928 cycles	AML, MDS	Not reported	8 episodes (3.2 %)	Risk for infection in general: low platelet counts, low hemoglobin, poor cytogenetics
Falantes, 2014 [38]	64 (72 % frontline); 523 cycles	AML, MDS	No	8 episodes (12.5 %, aspergillosis 6, candidiasis 2)	Higher rate if IFD in patients receiving prior chemotherapy
Ofran, 2015 [38]	173;	AML, MDS; AZA for 5 or 7 days	Not reported	2 episodes (1.1 %)	Risk for infection in general: low platelet counts, azacitidine 7 days
Pomares, 2016 [42]	121 (96 % frontline); 948 cycles	AML, MDS	No	2 episodes (1.6 %)	No recommendation for prophylaxis
Bainschab, 2016[34]	40	AML, MDS (a few patients treated with LDAC)	No	No episode	
Ali, 2017[33]	85; 282 cycles	AML, MDS	68 cycles (fluconazole 51)	2 episodes (2.3 %)	
Lorenzana, 2017[36]	76; 283 cycles	AML, MDS	Anti-mold prophylaxis in 60 patients	2 episodes (2.6 %)	Antimicrobial prophylaxis decreased the risk of infection overall
Trubiano, 2017[39]	68;884 cycles	AML, MDS	30 % of cycles, mostly anti-mold	7 episodes (10.3 %); aspergillosis 5	Risk for infection: very high IPSS-R score
Kim, 2020[40]	203	AML, MDS, CMML	Fluconazole in 23 patients. Excluded if anti-mold prophylaxis	7 episodes (3.4 %)	More IFD if neutropenia at start of cycle, therapy-related MDS
Wang, 2022 [41]	38 (analysis with 23 patients receiving VEN + AZA	AML	Fluconazole in 1 and posaconazole in 2 patients	6 episodes (15.8 %); all aspergillosis	Risk of IFD: unfavorable ELN risk group, prolonged neutropenia

IFD = invasive fungal disease; MDS myelodysplasia; AML = acute myeloid leukemia; AZA = azacitidine; IPSS-R = revised International Prognostic Scoring System; CMML = chronic myelomonocytic leukemia; ELN = European Leukemia Net; VEN = venetoclax

is appropriate, especially because mold-active azoles (voriconazole and posaconazole) may cause significant toxicity (notably liver toxicity) [13,14], and drug interactions between venetoclax and azoles may be a problem [15]. Moreover, the risk factors for IFD in patients receiving intensive induction remission regimens [16] may not apply to those receiving venetoclax plus azacytidine. In this paper we will review the incidence and risk factors for IFD in patients with AML receiving intensive chemotherapy, azacitidine monotherapy or in combination with venetoclax, and will reflect on the need of antifungal prophylaxis and if it is possible to stratify the risk of IFD in such patients. Finally, we will come with suggestions on how to manage these patients if primary anti-mold prophylaxis is not given.

2. Risk factors for invasive fungal disease in patients receiving intensive chemotherapeutic regimens

The risk of IFD in AML is mainly driven by the intensity and duration of neutropenia [1,16]. The delay in neutrophil recovery occurs in patients with induction failure increases the risk of IFD and of treatment-related mortality [17]. Thus, an assessment of pretreatment parameters that may reduce the chance of obtaining complete remission with conventional intensive chemotherapy (7 + 3 regimen) may help to assess the risk of IFD [16,18,19]. Factors associated with induction failure include older age, high white blood cell counts, secondary leukemia, adverse cytogenetic and molecular profiles, and residual blasts in the bone marrow on day 15 of induction [20–23]. Furthermore, mucositis following intensive regimens (high dose cytarabine), increases the risk of invasive candidiasis [24,25]. Other factors that should be considered when performing risk stratification of IFD in AML are poor performance status, receipt of corticosteroids, some comorbidities such as chronic obstructive pulmonary disease, smoking, high body weight, iron overload and hyperglycemia, and environmental exposure (rooms with or without HEPA filter, building construction or renovation) [18,26–30]. As pointed out, all these risk factors were established in AML

Table 2
Studies reporting invasive fungal disease in patients receiving venetoclax + hypomethylating agents in acute myeloid leukemia.

Author, year	Number of patients	AML ND vs. R/R	AML subtype	Antifungal prophylaxis	Proven or probable IFD	Predictors of IFD
Aldoss, 2019[45]	119	ND 46 %, R/R 54 %	De novo 53 %, secondary 28 %, therapy-related 19 %	Overall, 67 %; micafungin 38 %, azoles 41 %	12.6 %; all caused by molds (aspergillosis 7)	No CR/CRi, R/R leukemia
Lee, 2021 [47]	122	ND 32 %, R/R 68 %	De novo 79.5 %, secondary 17.2 %, therapy-related 3.3 %	Overall, 88.4 %; fluconazole 98.1 %, posaconazole 1.9 %	18 %; all of aspergillosis	Secondary or therapy-related AML
Chen, 2022 [46]	131	All ND	De novo 29 %, secondary 50 %, therapy-related 6.1 %	Overall, 16.3 % (azoles)	3 %; candidemia 2, aspergillosis and fusariosis (1 each)	Poor patient fitness, TP53 mutation
On, 2022 [48]	235	ND 54.5 %, R/R 45.5 %	De novo 49.8 %, secondary 50.2 %	Overall, 67.2 %; azoles 60 %, echinocandin 5 %	5.1 %; aspergillosis 4, candidiasis 3	None
Zhang, 2022[49]	144	All ND	De novo 24 %, secondary 41 %	7.6 % (10 patients); anidulafungin 6, fluconazole 4, isavuconazole 1	5.5 %	None
Wang, 2022[41]	23	ND 82.6 % R/R 17.4 %	De novo 52.2 %, secondary 47.8 %	Overall, 78.3 %; posaconazole 73.9 %	26.1 %; aspergillosis 5, fusariosis 1	Unfavorable ELN risk group, prolonged neutropenia

AML = acute myeloid leukemia; ND = newly diagnosed; R/R = relapsed/refractory; IFD = invasive fungal disease; CR = complete response; CRi = complete response with incomplete hematologic recovery; ELN = European Leukemia Net

patients treated with intensive chemotherapeutic regimens.

3. Invasive fungal disease in patients receiving hypomethylating agents

Until recently, hypomethylating agents in monotherapy were considered standard of care for patients with AML not eligible for intensive induction regimens and for those with high-risk MDS [31,32]. The incidence of proven or probable IFD in this population has ranged from zero to 15.8 % (Table 1), and the role of antifungal prophylaxis is still controversial [33–42]. This wide variation in the incidence of IFD reflects the heterogeneity of patients' populations (different proportions of patients with AML or MDS, different status of the disease, etc.) and probably the influence of local epidemiology.

Variables associated with a higher frequency of IFD were identified in three studies: unfavorable European Leukemia Net risk group and prolonged neutropenia in one study [41], neutropenia at start of the cycle and therapy-related MDS in the second study [40], and prior chemotherapy before the use of hypomethylating agents in the other study [35].

4. Invasive fungal disease in patients receiving less intensive venetoclax-based regimens

Two randomized trials evaluated the combination of venetoclax with low-dose cytarabine [43] or with azacitidine [12]. None of these studies reported the incidence of IFD. In a previous study, 145 AML patients were treated with venetoclax at different doses (400 mg, 800 mg or 1200 mg/d) plus azacitidine or decitabine. The concomitant use of moderate or strong CYP3A4 inhibitors (including azoles) was not allowed. Grade ≥ 3 IFD was observed in 9% of patients (8% grade 3–4 and 1 fatal case) [44]. Since then, a few retrospective and real-life studies reported the incidence of IFD in patients treated with venetoclax-based regimens, with incidences ranging from 3 % to 26.1 % (Table 2) [41, 45–49]. In a study with 119 AML patients, probable or proven IFD was more frequent among non-responders (22 % vs 6 %,) and in relapsed or refractory (R/R) patients compared with newly diagnosed AML (19 % vs 5 %) [45]. In a study from South Korea with 122 patients, mortality rates were higher in patients with IFD (63.6 % vs 39.0 %) and the only risk factor for IFD was secondary or therapy-related AML [47]. In other study, among 131 AML patients, predictors of IFD were poor performance status and mutation in the *TP53* gene. Antifungal prophylaxis had no impact on IFD or overall survival, and the authors concluded that antifungal prophylaxis is not necessary in institutions with low incidence of IFD [46]. Two other studies with low incidences of IFD (5.1 % and 5.6 %) also concluded that antifungal prophylaxis may not be necessary for all patients undergoing treatment with venetoclax-based regimens [48,49].

Based on the data from these studies, AML patients receiving venetoclax-based regimens are more likely to develop IFD in the setting of: (1) relapsed/refractory disease; (2) secondary or therapy-related disease; (3) presence of *TP53* mutation; (4) poor patient fitness; and (5) no response to therapy.

5. Problems with antifungal prophylaxis

Primary antifungal prophylaxis with an azole is a well established practice in the management AML patients receiving intensive induction chemotherapy [8]. However, there are various potential problems associated with the use of azoles including toxicity, drug-drug interactions, development of resistance and erratic serum levels requiring therapeutic drug monitoring. The main side-effects associated with azoles are liver toxicity, QTc prolongation, visual disturbances, neurological and gastrointestinal toxicities [50,51]. In a multicentric registry of 2009 patients who received azoles in 55 centers in the USA, 14.7 % of patients had adverse drug reactions, especially with voriconazole and posaconazole (14.2 % and 11.3 %, respectively). The most frequent toxicity was hepatic, occurring in 7.3 % of patients overall (8.1 %, 5.9 % and 1.2 % of patients receiving voriconazole, posaconazole and isavuconazole, respectively) [13]. In other study, 277 patients with AML were treated with intensive chemotherapy (62 %) or venetoclax-based regimens (38 %) and received azole prophylaxis (posaconazole 51 %, voriconazole 30 %, isavuconazole 19 %). Discontinuation due to toxicity (mostly hepatic) occurred in 14 %, with similar rates of discontinuation between the azoles (13 %, 15 % and 13 % for posaconazole, voriconazole and isavuconazole, respectively) [14].

Azole antifungals are metabolized by cytochrome P450 and are potent inhibitors of CYP34A enzymes, especially CYP3A4 [52]. Venetoclax is metabolized by CYP3A4 and P-glycoprotein and when administered together with moderate or strong inhibitors of CYP3A4 such as posaconazole, voriconazole and isavuconazole, a reduction in the dose of venetoclax is recommended (50 % of the full dose with moderate and 25 % with strong CYP3A4 inhibitors) [53].

A study evaluated the time to neutrophil recovery ($>1000/mm^3$) and platelet recovery ($>100,000/mm^3$) in 64 AML patients who achieved response after one course of venetoclax plus an hypomethylating agent, comparing 47 patients who were on azole prophylaxis (posaconazole in 17, voriconazole in 9, isavuconazole in 20, fluconazole in 1) with 17 who did not receive prophylaxis with an azole. The time to neutrophil recovery was not different in the two groups, but the time to platelet recovery was significantly longer in patients on azole prophylaxis (28 vs. 22 days) [54].

A post-hoc analysis of the Viale-A study evaluated the effect of concomitant use of CYP3A4 inhibitors in the first two cycles of treatment on efficacy and safety. Among 293 patients receiving venetoclax plus azacitidine, 41 (14.3 %) received moderate CYP3A4 inhibitor and 22 (7.7 %) received strong CYP3A4 inhibitor. The concomitant use of CYP3A4 inhibitor had no influence on response rates (67 %, 61 % and 64 % with no, moderate, or strong inhibitor, respectively) or overall survival (15.2 months, 12.3 months, and 12.2 months with no, moderate, or strong inhibitor, respectively). There was no comparison between patients receiving azoles or echinocandins as antifungal prophylaxis [55].

In another study, the venetoclax exposure-efficacy and exposure-safety relationships was evaluated in patients with newly diagnosed AML receiving venetoclax with low-dose cytarabine or with hypomethylating agents. In patients receiving venetoclax plus hypomethylating agents, there was a trend for higher probability of grade ≥ 3 infection with increasing exposure: 51% probability of infection with 400 mg/d and 59 % with 800 mg/d. While doses of 400 mg/d, 600 mg/d and 800 mg/d had similar probabilities of neutrophil recovery, the dose of 400 mg/d had higher probability of platelet recovery. In addition, increasing concentration of venetoclax up to 400 mg/d had significantly higher probability of response compared with lower doses [56]. These data suggest that underexposure to venetoclax may be associated with a lower probability of response, and overexposure may result in a slight increase in the risk of infection. Therefore, if venetoclax is combined with voriconazole or posaconazole, variations in the serum levels of the azoles may result in under or overexposure to venetoclax. This may be more problematic with voriconazole where serum levels are not predictable from one patient to the other because of the polymorphism in CYP2C19 [57]. Indeed, therapeutic drug monitoring is generally recommended for posaconazole and voriconazole [58].

6. How we manage patients with acute myeloid leukemia treated with venetoclax-based regimens

Based on clinical experience and real-world studies already published [41, 45–49], we think that antifungal prophylaxis should not be given to all AML patients treated with venetoclax-based regimens (hypomethylating agents or low-dose cytarabine). First, drug-drug interactions are a concern and may have an impact on venetoclax exposure, potentially decreasing its efficacy and increasing toxicity. Second,

Table 3
Risk stratification of invasive fungal disease in patients with acute myeloid leukemia receiving less intensive venetoclax-based regimens.

Factor	Low-risk	High-risk
Leukemia-related		
Prior chemotherapy	No	Yes
Status of AML	Newly diagnosed	Relapsed / refractory
ELN risk stratification	Favorable	Unfavorable
Type of AML	De novo	Secondary or therapy-related
Neutropenia at start of cycle	No	Yes
Probability of response	High	Low
TP53 mutation	No	Yes
Host-related		
Performance status / fitness	Good	Poor
Chronic obstructive lung disease	Absent	Present
Active smoking	No	Yes
Body weight	Low	High
Iron overload	No	Yes
Hyperglycemia	No	Yes
Environmental factors		
Room	HEPA filter and positive pressure	No HEPA filter
Heavy dust exposure	No	Yes
Other factors		
Receipt of corticosteroids	No	Yes
Local epidemiology	High incidence of IFD	Low incidence of IFD

AML = acute myeloid leukemia; ELN = European Leukemia Net; HEPA = high efficiency particulate air; IFD = invasive fungal disease

azole antifungal agents have several side effects (particularly liver toxicity) that may complicate the treatment of AML. Third and most important, because the incidence of IFD varies across institutions and is probably lower with venetoclax-based regimens compared with intensive chemotherapy. Instead of giving anti-mold prophylaxis to all patients, a selection of patients at higher risk could be a wiser strategy, considering factors associated with an increased risk of IFD in patients receiving hypomethylating agents with or without venetoclax. Pre-treatment factors that should be included in a risk stratification strategy include prior chemotherapy [35], neutropenia at start of cycle, unfavorable ELN risk group [41], low probability of achieving complete response, R/R AML [45], secondary or therapy-related AML [47], *TP53* mutation and poor patient fitness [46]. In addition, local epidemiology should be strongly considered. Finally, previously defined risk factors for IFD in AML patients such as receipt of corticosteroids, comorbidities (chronic obstructive pulmonary disease, smoking, high body weight, iron overload, hyperglycemia), and environmental exposure (rooms with or without HEPA filter, building construction or renovation) should be taken into consideration [18, 26–30] (Table 3).

Finally, if we dont give anti-mold prophylaxis in AML to all patients who will receive a venetoclax-based regimen, how do we manage these patients? The first consideration is to increase the awareness for IFD, taking into consideration local epidemiologic aspects. If the patient is treated in the hospital, serial (2–3 times per week) serum galactomannan is a good strategy to early diagnose invasive aspergillosis [16]. Alternatively, serum galactomannan should be part of the initial workup for fever. In addition, chest CT scan should be obtained in patients with respiratory symptoms or in case of persistent or recurrent fever during neutropenia. Other tests should be considered depending on local epidemiology.

In conclusion, the treatment of AML has improved with the discovery of targeted drugs, bringing new challenges in the management of these patients. Invasive fungal disease is still a threat in this population, but we think that a risk stratification strategy is a wiser way to approach this problem. More studies are needed to better characterize the epidemiology of IFD in AML patients treated with venetoclax-based regimens and with other targeted drugs.

Funding

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

Declaration of Competing Interest

M.N. has received honoraria as consultant or speaker from Knight, Pfizer, Abbvie, Teva, Cidara, F2G, Abbott, Janssen, MSD, Astellas, Pharmalab, GSK, Takeda, AstraZeneca, and Zodiac. M.G. has no conflicts to disclose.

Acknowledgments

None.

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APÊNDICE 4

Artigo 4: “EQUAL Fusariosis score 2021: An European Confederation of Medical Mycology score derived from current guidelines to measure QUALity of the clinical management of invasive fusariosis”

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Article type : Original Article

EQUAL Fusariosis Score 2021: An **E**uropean Confederation of Medical Mycology score derived from current guidelines to measure **QUAL**ity of the clinical management of invasive fusariosis

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Running title: EQUAL score Fusariosis

Conflict of interest statement: MN reports personal fees from Pfizer, MSD, Astellas, Biotoscana, Basilea, Abbvie, Janssen, Amgen, Teva and Abbot outside the submitted work. All other authors have nothing to disclose.

Ethics statement: The authors confirm that the ethical policies of the journal, as noted on the journal's author guidelines page, have been adhered to. No ethical approval was required as the research in this article related to micro-organisms.

Data Availability Statement: Data sharing not applicable to this article as no datasets were generated or analysed during the current study

This article has been accepted for publication and undergone full peer review but has not been through the copyediting, typesetting, pagination and proofreading process, which may lead to differences between this version and the Version of Record. Please cite this article as doi: 10.1111/MYC.13321

Abstract

Background: Invasive fusariosis is a serious infection affecting mostly patients with hematologic malignancies and hematopoietic cell transplant recipients.

Objectives: To develop a scoring tool that evaluates guideline adherence in the management of invasive fusariosis.

Methods: We reviewed two guidelines, provided by the European Society for Clinical Microbiology and Infectious Diseases (ESCMID) and the European Confederation of Medical Mycology (ECMM), and selected the strongest recommendations for management quality as the bases for the scoring tool.

Results: We reviewed the recommendations regarding primary and secondary prophylaxis, diagnostics procedures (images, blood cultures, biopsy of skin lesions with direct exam, culture and histopathology, species identification, antifungal susceptibility tests and antigen detection), treatment choices and follow-up procedures. The tool comprises 18 items, with a maximum of 24 points.

Conclusions: The EQUAL score Fusariosis is a tool that may help clinicians to measure guidelines adherence.

Keywords: fusariosis; Fusarium; score; guideline; stewardship; fungal infection; invasive mycosis; invasive fusariosis

Introduction

Invasive fusariosis is a serious infection that affects mostly patients with severe immunosuppression, particularly neutropenic patients with acute leukemia and hematopoietic cell transplant (HCT) recipients.[1] In such patients, the disease is usually disseminated, with typical metastatic skin lesions, positive blood cultures and poor outcome.[2] The most frequent species causing invasive fusariosis are *Fusarium solani* species complex (FSSC) and *Fusarium oxysporum* species complex (FOSC).[3] In addition to disseminated disease, pneumonia is frequent, and may have a clinical presentation similar to invasive aspergillosis, including macronodules with or without halo sign and positive serum galactomannan.[4] Beta-glucan is frequently positive in cases of disseminated disease.[5] Blood cultures and skin biopsy with direct exam, culture and histopathology, are the most frequent sources of diagnosis of invasive fusariosis.[6] *Fusarium* species usually exhibit high minimum inhibitory concentrations (MICs) to most antifungal agents including voriconazole, posaconazole, isavuconazole and amphotericin B.[7] However, a clear-cut correlation between MIC and outcome has not been established,[8] as illustrated by the good clinical response to voriconazole despite the high MICs exhibited in the susceptibility test studies.[9, 10] Treatment options for invasive fusariosis include a lipid formulation of amphotericin B and voriconazole.[10] Immune reconstitution is a key prognostic factor, with poor outcome in persistently neutropenic patients regardless of the antifungal regimen.[1]

Recently, the European Confederation of Medical Mycology (ECMM) together with the International Society for Human and Animal Mycology (ISHAM) and the American Society for Microbiology (ASM) published a guideline for the diagnosis of rare moulds, including fusariosis.[11] In this paper, we present a score which reflects the strongest recommendations from these guidelines. The application of this score system allows clinicians and hospitals to quantify guideline adherence, and to support antifungal stewardship programs.

Methods

We review two guidelines presenting recommendations for the management of invasive fusariosis: the guidelines published in 2014 by the European Society for Clinical Microbiology and Infectious Diseases (ESCMID) and the European Confederation of Medical Mycology (ECMM),[12] and the global guidelines for the diagnosis and management of rare mold infections, developed by the ECMM, the International Society for Human and Animal Mycology (ISHAM), and the American Society for Microbiology (ASM), which represents an update and extension of the pervious guidelines.[11] First, we grouped recommendations into prophylaxis, diagnosis,

treatment and follow-up. Then, we selected 'A' to 'C' recommendations as an ideal management approach to a hypothetical patient. In the last step we allocated score points along the guideline levels of evidence and the clinical importance regarding the management of patients. Since the prompt determination of the correct diagnosis is very important in order to improve the outcome, more points or relative weight were given to the diagnostic section of the score. We subdivided this section into subsections of imaging, direct exam and culture of blood and skin lesions (the most frequent clinical presentation in cases of disseminated disease), histopathology, serology tests, species identification and susceptibility tests, acknowledging that the two latter are not strictly necessary for treatment decisions. The treatment section comprised the first line options and ancillary therapies, with surgical debridement of necrotic material, and the use of granulocyte transfusion and granulocyte colony-stimulating factor (GCSF) or granulocyte-monocyte colony-stimulating factor (GM-CSF). The follow-up section comprised only serum galactomannan to monitor treatment response.

Results

The recommendations, levels and strengths of evidence and scores are summarized in the Table. Patients with neutropenia or HCT recipients with positive culture for *Fusarium* species in superficial skin lesions in the extremities (interdigital intertrigo and /or onychomycosis) should receive mould active prophylaxis (voriconazole or posaconazole) (1 point). Patient who had invasive fusariosis and will be exposed to a subsequent period of immunosuppression (neutropenia and / or T-cell immunodeficiency) should receive secondary prophylaxis with voriconazole, posaconazole or a lipid formulation of amphotericin B (liposomal or lipid complex) (1 point)

In neutropenic patients with unexplained persistent or recurrent fever despite broad-spectrum antibiotics, blood cultures should be obtained (2 points) and chest and sinuses computerized tomography (CT) should be performed (2 points). In the presence of skin lesions (papular or nodular erythematous with central necrosis), biopsy is mandatory. Direct microscopic exam of skin biopsy (2 points) is the fastest and easiest way to establish a presumptive diagnosis of invasive fusariosis before the results of culture and histopathology are available. Culture (2 points) and histopathology (2 points) of skin or other tissue are strongly recommended. Serology tests with fungal antigen detection such as aspergillus galactomannan antigen test (1 point) and 1,3-beta-D-glucan (1 point) may be positive before the clinical manifestations of invasive fusariosis. In case of growth of *Fusarium* in culture, species identification can be performed with MALDI-TOF or PCR (1 point), although this is more important for epidemiological aspects than

for defining treatment. The same is true for antifungal susceptibility tests, using EUCAST or CLSI (1 point).

First-line treatment for invasive fusariosis comprises a lipid formulation of amphotericin B (liposomal amphotericin B or amphotericin B lipid complex) or voriconazole (2 points). Combination therapy with voriconazole plus a lipid formulation of amphotericin B is another option (2 points). In patients with local infection with necrotic tissue (skin and soft tissues), surgical debridement is recommended (2 points). Ancillary measures to enhance immunity include granulocyte colony-stimulating factor (G-CSF), granulocyte-monocyte colony-stimulating factor (GM-CSF) and granulocyte transfusion (1 point). In addition, if positive at diagnosis, serum galactomannan is recommended to monitor treatment (2 points).

Discussion

The EQUAL (ECMM score to measure QUALity of clinical management) fusariosis score is an 18-item tool that gathers the most relevant recommendations from recent guidelines, and may help clinicians and institutions to quantify the quality of care of immunocompromised patients who develop invasive fusariosis. The score was created following the same procedures applied in other EQUAL scores.[13-16]

The pathway for the proper management of patients with invasive fusariosis starts with the identification of patients at risk. Invasive fusariosis occurs typically in patients with hematologic malignancies, especially those with acute leukemia with severe neutropenia and HCT recipients with neutropenia or graft versus host disease.[10] Among neutropenic patients, fusariosis usually manifests as disseminated disease, with persistent or recurrent fever despite appropriate antibiotic therapy, and the sudden appearance of multiple skin lesions or pneumonia.[2] In this context, blood cultures and chest CT scans are mandatory. In patients with pneumonia, the differential diagnosis with invasive aspergillosis can be challenging, especially because serum galactomannan is frequently positive in invasive fusariosis.[4] Positive blood cultures and / or the appearance of skin lesions point to the diagnosis of fusariosis. Once the diagnosis is established, molecular and mass spectrometry methods are helpful in species identification. However, since these methods are not widely available and because species identification adds little to treatment decisions, we gave 1 point for these procedures. The same is true for antifungal susceptibility tests, since there is no correlation between MIC and the outcome.[8] There are no randomized studies evaluating different treatment regimens for the treatment of invasive fusariosis. Furthermore, although recovery of immunity is the main prognostic factors, the role of adjunctive therapies such as G- or GM-CSF

and granulocyte transfusions in the treatment is not clear. The EQUAL Fusariosis score reflects these limitations.

The maximum EQUAL Fusariosis score may vary according to the host (neutropenic or non-neutropenic), presence of skin lesions in the extremities with positive culture for *Fusarium* species, clinical presentation (fungemia, single organ involvement such as pneumonia, or disseminated disease), source of diagnosis (blood cultures, skin biopsy), treatment response and subsequent periods of immunosuppression. Considering a hypothetical patient who presents with onychomycosis with positive culture for *Fusarium* species, becomes neutropenic, develops disseminated disease with skin lesions and positive blood cultures, have successful treatment and receives subsequent cycles of chemotherapy, the maximum score will be 24.

The development of guidelines is important to help clinicians in the proper management of many clinical conditions, especially in relatively uncommon diseases like invasive fusariosis. However, the adherence to guidelines recommendations may be challenging, with many different recommendations. The EQUAL score Fusariosis is a tool that may help clinicians to measure guidelines adherence.

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Table: EQUAL score Fusariosis items with strengths of recommendations and levels of evidence

	Quality indicator	Strength of recommendation	Level of evidence	Equal score points
Primary prophylaxis	Neutropenic patient or HCT recipient positive culture for *Fusarium* species in superficial skin lesions in the extremities (interdigital intertrigo and /or onychomycosis). Drug of choice: voriconazole or posaconazole	B	IIu	1
Secondary prophylaxis	Patients with previous invasive fusariosis who will receive treatment that induces neutropenia or severe T-cell immunodeficiency. Drug of choice: voriconazole, posaconazole or a lipid formulation of amphotericin B	B	IIu	1
Diagnosis	Chest/Sinus CT in the case of persistent or recurrent fever (fusariosis less likely to have halo sign)	A	IIh	2
	Blood cultures	A	IIu	2
	Skin (more frequently) or other tissue			
	Direct exam	A	IIu	2
	Culture	A	II	2
	Histopathology	A	II	2
	Serology			
	Serum galactomannan serum	B	IIu	1
	Serum 1,3-beta-D-glucan	C	II	1
	Species identification			
	PCR or MALDI-TOF MS	B	IIu	1
	Antifungal susceptibility tests (CLSI or EUCAST)	C	IIu	1
Treatment, fist line	Voriconazole IV, switch to PO once stable	A	IIu	2
	Liposomal amphotericin B or amphotericin B lipid complex	A	IIu	2
	Combination therapy with voriconazole and a lipid formulation of amphotericin B	A	IIu	2
Ancillary therapies	Surgical debridement of necrotic tissue	A	II	2
	G-CSF or GM-CSF	B	IIu	1
	Granulocytic transfusions	C	III	1
Follow-up	Galactomannan in serum (if positive at diagnosis)	A	II	2

HCT = hematopoietic cell transplantation; CT: computerized tomography; PCR = polymerase chain reaction; MALDI-TOF MS = matrix assisted laser desorption ionization-time of flight mass spectrometry; CLSI = Clinical and Laboratory Standards Institute; EUCAST = European Committee on Antimicrobial Susceptibility Testing; IV = intravenous; PO = per os; G-CSF = granulocyte colony-stimulating factor; GM-CSF = granulocyte-monocyte colony-stimulating factor

u = comparator group, uncontrolled trials; h = comparator group, historical controls

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